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AND

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INTERNATIONAL RECORD OF MEDICINE
In Quest of the Broad Spectrum — *Filix Martí-Ibáñez*

SYMPOSIA ON NEW FACTS AND PERSPECTIVES OF BROAD-SPECTRUM ANTIBIOTIC THERAPY
I—OXYTETRACYCLINE
Guest Editor—Merle M. Musselman, M.D.
Part I

Introduction — *M. M. Musselman*
Antimicrobial Activity, Pharmacology, Chemistry, and Clinical Uses of Oxytetracycline — *M. M. Musselman and H. L. Davis*
Oxytetracycline in General Medicine — *Wallace E. Herrell*
Oxytetracycline in Pediatrics — *William J. Farley*
Oxytetracycline in Tropical Medicine — *E. H. Loughlin and W. G. Mullin*
The Use of Oxytetracycline in the Treatment of Certain Tropical Diseases — *William W. Frye*

EDITORIAL SURVEY
Nutrition in Health and Disease

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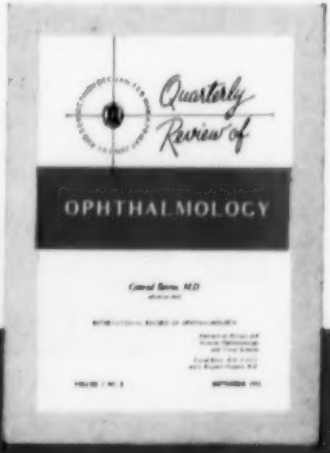

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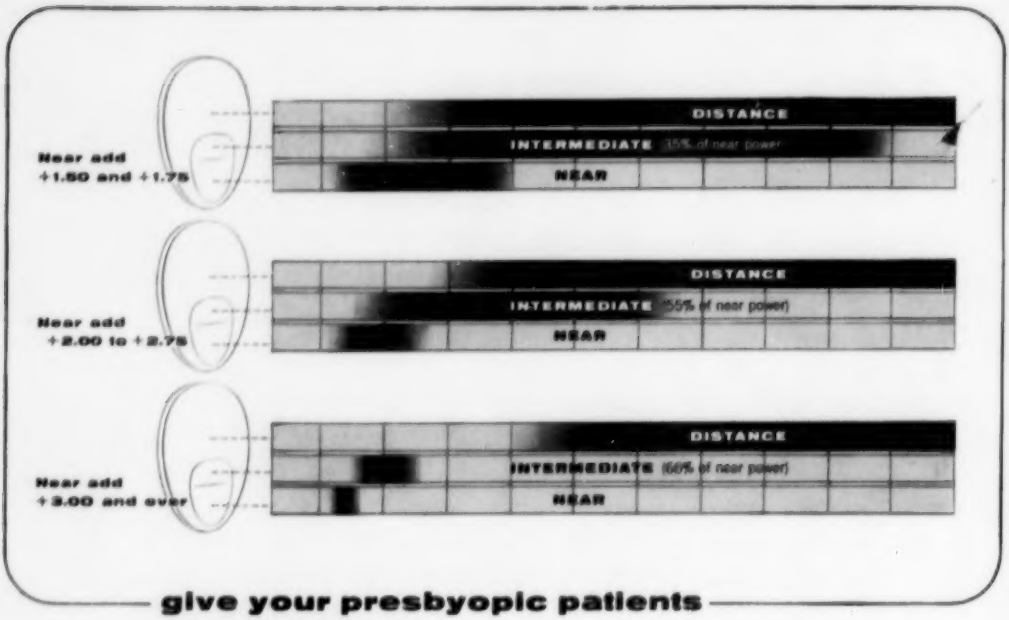

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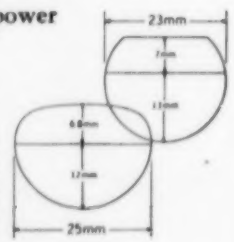

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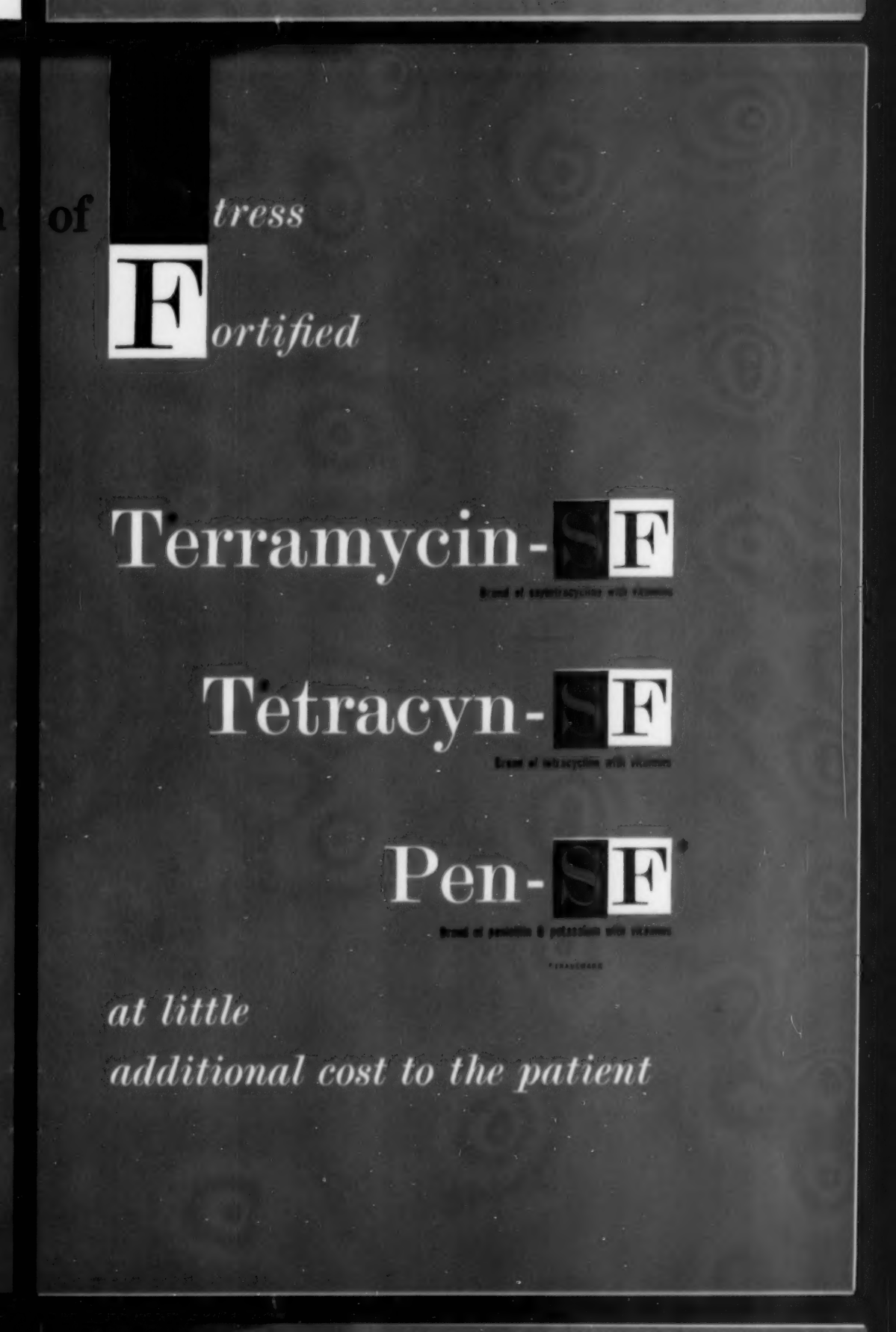
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In Quest of the Broad Spectrum 103
Félix Martí-Ibáñez

Symposia on New Facts and Perspectives of Broad-Spectrum Antibiotic Therapy
I—Oxytetracycline

Guest Editor—MERLE M. MUSSELMAN, M.D.

PART I*

Introduction 111
M. M. Musselman

Antimicrobial Activity, Pharmacology, Chemistry, and Clinical Uses of Oxytetracycline 112
M. M. Musselman and H. L. Davis

Biographical Note on Dr. Merle M. Musselman 131

Oxytetracycline in General Medicine 132
Wallace E. Herrell

Oxytetracycline in Pediatrics 140
William J. Farley

Oxytetracycline in Tropical Medicine 150
Elmer H. Loughlin and William G. Mullin

The Use of Oxytetracycline in the Treatment of Certain Tropical Diseases 169
William W. Frye

EDITORIAL SURVEY

Nutrition in Health and Disease 178

GENERAL PRACTICE CLINICS

Progress in the Clinical Diagnosis of Poliomyelitis 180
Russell J. Blattner

Nutrition in Congestive Heart Failure 181
M. D. Wohl and C. R. Shuman

* Part 2 of the **Symposia on New Facts and Perspectives of Broad-Spectrum Antibiotic Therapy** will be published in the *International Record of Medicine*, April, 1955. The following articles will be presented in Part II:

OXYTETRACYCLINE IN DERMATOLOGY AND SYPHILOLOGY
by Harry M. Robinson, Jr., M.D.

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J. Buchman, M.D.

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Aaron Prigot, M.D., and Aubre de L. Maynard, M.D.

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H. Close Hesseltine, M.D.

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OXYTETRACYCLINE IN OPHTHALMOLOGY: A REVIEW OF THE LITERATURE
Joseph W. Hallett, M.D., and Irving H. Leopold, M.D.

Quarterly Review of **OPHTHALMOLOGY**

Incorporating the International Record of Ophthalmology

OPHTHALMOLOGY ABSTRACTS

Anatomy, Embryology, Heredity, Development and Nutrition

Heredity and the Eye 185

Ocular Movements and Motor Anomalies, Nystagmus Reading Disability

Treatment of Paralysis of the Extra-Ocular Muscles 185

Anomalies of Refraction and Accommodation, Contact Lenses

Contact Lenses: Statistical Evaluation of Tolerance 186
The Design and Development of a Contact Lens for Underwater Seeing 186
The New Contact and Corneal Lenses 186

Conjunctiva

A New Trachoma Concept 187

Cornea, Sclera and Tenon's Capsule

Malignant Melanoma of the Cornea 189

Retina

Motions of the Retinal Image during Fixation 189
Diathermic Treatment of Different Forms of Retinal Detachment and Results 190
Vascular Disturbances in the Retina of Diabetic Patients 190
Clinical and Therapeutic Considerations of Detachment of the Retina 190
Macula: Alteration of the Vascular Arrangements in Arteriosclerosis 190
Cerebral Vessels and Retinal Vessels 191
Effect of Oxygen on Developing Retinal Vessels with Particular Reference to the Problem of Retrolental Fibroplasia 191
Direct Observation of the Effect of Oxygen on Developing Vessels (Preliminary Report) 192
Pathological Basis of Retrolental Fibroplasia 193

Eyelids

Correction of Upper Lid Blepharochalasis 193

Anesthesia

Curare in Ophthalmology 193

Medical Ophthalmology

The Relationship between the Severity and Care of Diabetes Mellitus and the Incidence of Diabetic Retinopathy 194
Numerical Evaluation of Ocular Signs of Essential Hypertension 194

Illumination and Illuminating Engineering

The Effect of Veiling Luminance upon the Apparent Brightness of an Object 194

Miscellaneous

Reading—A Developmental and Educative Process 195
A System of Communication in Occupational Optometry 195
Education for Survival 196
A New Buried Movable Orbital Implant 196
A Registering Low-Level Photometer 196
School Lighting and Posture 196
Clinical Experience with Hard Resin Lenses 197

BOOK REVIEWS

Travaux d'Anatomie Pathologique Oculaire 197
Differential Diagnosis of Common Diseases of the Eyeground 198

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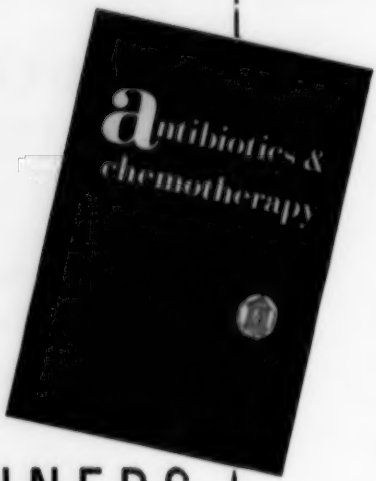

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In Quest of the Broad Spectrum

SOME PHILOSOPHICAL PERSPECTIVES OF ANTIBIOTICS

Félix Martí-Ibáñez, M.D.

NEW YORK, N. Y.

THE PRECURSORS OF ANTIBIOTIC THERAPY

Life is an awe-inspiring biological symphony made possible by the activity of some symbiotic bacteria indispensable to human life. For instance, the intestinal flora bacteria which, through their symbiotic action, produce certain substances necessary for hematopoiesis. But there are also pathogenic germs in the world of man, and against these deadly enemies he has developed a rich and powerful chemotherapeutic arsenal.

For almost two thousand years, from Hippocrates to Pasteur, man tried to fight infection with magical and empirical weapons. In the beginning he attempted to expel the causal agents of infection—regarded at first as demons, later as miasmas, and finally as germs—by means of prayers, herbs, or the magic metals of Paracelsus, the founder of medicinal chemistry. Next, man progressed to the point of attacking infectious diseases with serums and vaccines, thus reinforcing the natural organic defenses. And then, one memorable day in the history of Medicine, a French veterinarian threw the window open and let in the light of the microbial doctrine of infection.

If, according to the age-old saying, all roads lead to Rome, all paths in Bacteriology lead back to Pasteur. The work done by Pasteur (1882–1895) and Koch (1843–1910) established the bases of medical microbiology. Although Pasteur did little in the field of Chemotherapy, his work stimulated Lister's research into the problem of septic wounds which obsessed not only him but all surgeons a century ago. Twenty years before Lister, in 1847, Semmelweis had already introduced the idea of disinfecting the surgeon's soiled hands with calcium chloride to prevent puerperal fever. His contribution initiated the development of the three great methods to fight in-

fection: disinfection; antisepsis, which would later become asepsis; and chemotherapy.

In his crusade against "putrefaction" of operative wounds, Lister adopted carbolic acid sprays as his principal weapon for preventing bacteria from reaching operative wounds by first destroying them in the air. This led subsequently to the use of hydrosoluble chemotherapeutic agents. The antisepsis introduced by Lister in 1867, however, was very limited in scope because it allowed for the destruction of the bacterial enemy only *before* it invaded the body and penetrated into the tissues. That is why such antisepsis was later replaced by asepsis, a true prophylactic chemotherapy that made use of chemical substances to treat infections that had already taken root. These substances, however, proved to be active only in superficial infections and were even more toxic to the tissues than to the bacteria. But the philosophical principle that guided Lister still prevails in surgery. For if the sterilization of instruments is fundamentally a method availing itself of heat as a *physical* agent, the disinfection of the skin and wounds must be carried out through *chemical* agents.

Twenty years (1847–1867) elapsed between Semmelweis' and Lister's discoveries. After Lister came half a century of scientific groping in the dark, until, in 1909, Ehrlich's chromotherapy with salvarsan ushered in the age of chemotherapy in bacterial infections. Ehrlich's "magic bullets," however, hit only limited targets. Twenty-six years later Domagk introduced the sulfonamides, which enabled the physician to put the bacteria "to sleep," thus arresting their development and enabling the leukocytes to sweep them out with the brooms of their pseudopods. The sulfonamides were useful as a systemic treatment, but they showed poor results when used topically, since their powers were neutralized in those great leukocyte graveyards—the pus of septic wounds.

Twenty-six years later, when some humble Penicillium spores fell from smoky gray skies onto a culture plate in a London hospital, there was planted—not only on the plate but in Fleming's mind—the seedling that was later to grow into the wonder crop of antibiotics.

IN QUEST OF THE BROAD SPECTRUM

The history of man's struggle against infection is one of incessant, almost agonizing, searching for a drug endowed with a broad antimicrobial spectrum. Having progressed beyond the ancient Greek dream of the universal panacea and the medieval dream of the philosopher's stone, medical researchers from Pasteur on were aware of what infection represented and applied themselves to seeking a drug that had a wide therapeutic horizon and a deep healing effect; in other words, a drug capable of curing the maximum number of infections with a minimum risk to the patient.

The pharmaceutical cavalcade that began in the middle of the last century was discouraged at first: it was thought impossible to find a drug with a broad antimicrobial spectrum, because common belief held that human and bacterial protoplasms were so similar that any chemical agent which destroyed one would necessarily harm the other. Malaria was finally and successfully treated with quinine, and syphilis with Ehrlich's arsenicals, but medical opinion was that such chemo-

therapy was a lucky accident which could not be applied to virus and bacterial infections. The subsequent discovery of the sulfonamides, synthetic antimalarials, and antibiotics led slowly to that ideal pharmacological horizon of the broad antimicrobial spectrum. And when the myth of the identity of the protoplasms of human and microbial cells was finally destroyed, the dike that for so many years had obstructed the course of the mighty river of antibacterial chemistry was carried away.

Broad-spectrum antibiotics like oxytetracycline, the subject of this symposium, represent the crystallization of man's dream of a chemotherapeutic agent that would prevent the multiplication of invading germs and would destroy them without altering the function of organic cells.

"Old" antiseptics were a form of rudimentary local chemotherapy, just as arsenicals were a specific chemotherapy; but the use of antibiotics, "substances of microbial origin endowed with antibiotic powers," has expanded the horizon of the clinician: horizontally—to embrace the broad antimicrobial spectrum—and vertically—to achieve depth of effect, properties which are indispensable in any agent that claims to have a "broad antimicrobial spectrum," that historical Holy Grail of the crusaders of Chemotherapy.

Antibiotics, a product of the moist alchemy of the earth and often of molds—those tiny gnomes of the vegetable kingdom—have had a tremendous philosophical impact on modern clinical medicine, a subject I have discussed at length on other occasions.*† The glowing dawn of the antibiotic age suffuses the sky of contemporary medicine. Present antibiotic therapy enables us to catch a glimpse of the end of the historical road where are inscribed, as on an honor roll, the diseases that for many a millenium scourged humanity and which antibiotic medicine will finally vanquish.

The introduction of antibiotics, especially the broad-spectrum antibiotics, has had three important consequences in modern clinical medicine: it has altered classical pathology; it has changed clinical diagnosis from pathogenic to etiological; it has simplified anti-infectious therapy.

ALTERATION OF CLASSICAL PATHOLOGY

Antibiotics have altered classical pathology because the process of disease, including infection, is a mutable reality which, like every living thing, evolves spontaneously. Sometimes, as happens in infections, because disease depends on living species, it is subject to the same changes and degenerations as the causative germs; furthermore, because disease is a parasitical reality of human life, it, in time, evolves along with human life itself, especially because of the persistent action of drugs and the highly effective hygienic measures of present-day therapeutics.

Because antibiotics intervene at the most subtle phases of metabolism and in the most delicate enzymatic actions of bacterial life, they provoke changes in the bacteria's biological cycle which have already been translated into radical changes in

*Martí-Ibáñez, F.: The philosophical impact of antibiotics on clinical medicine, Antibiotics Annual 1954-1955, New York, Medical Encyclopedia, Inc., 1955.

†Martí-Ibáñez, F.: Antibiotics today and the medicine of tomorrow, Antib. & Chemo. 5:21 (April, supp. 1) 1955.

the diseases they cause. Antibiotics have influenced the natural history of infections like syphilis, which, nowadays, even when not treated with antibiotics, follows its course without the old phagedenic ulcers; and like typhoid fever, which now hardly ever presents the large splenomegalies of the old classical form.

NEW ETIOLOGICAL ORIENTATION OF MEDICINE

Antibiotics have changed the concept of diagnosis in clinical medicine. Twenty years ago medical teachers and students everywhere were still overawed by the infinite variations in the subtle arts of clinical exploration, percussion, and auscultation. They delighted in lingering over the pathogenesis of a disease; they had plenty of time to debate the differential diagnosis of a syndrome, and they elaborated on the localization of the disease with the painstaking precision with which an Oriental miniaturist places every speck of color on his miniatures.

Today pathogenesis is more and more considered as a stopping-off point on the way to the great terminal station of etiology. Modern medicine is constantly becoming more etiological in its conceptions, more dynamic in its specific therapies—perhaps both—even at the risk of sacrificing the minute precision of anatomical localizations and clinical descriptions with which textbooks were embellished at the beginning of our century.

But the symptom in itself, its nuances and qualities, is not the important fact, for the only normal aspect of clinical pathology is its paradoxical abnormality. That is why it is of the utmost importance to consider rapidly the vast mural of syndromes and symptoms in clinical pathology and then proceed to disentangle the secret of its etiology, without which therapeutics today would be as empirical as they were in the times of Avicenna.

Today, we accept the indestructible unity of the entire organism and the physiological correlation between all organic processes, much more apparent in disease than in health. When an organ or system is ill, the entire body suffers. Recognition of that fact forces the physician in our age of supreme specialization to widen his clinical education. Modern techniques give greater breadth and depth to his control of the disease process. The modern physician learns all he can about general medicine, since his therapy is guided by that "etiological preoccupation" which is tantamount to his wish to treat the entire organism, even as he focuses therapy on the specific cause of the disease.

This new etiological orientation of Medicine has led to the appearance of the *etiological sign*, which has succeeded the *lesional sign* of former anatomical pathology and the *functional sign* of physiopathology. This new etiological sign is sometimes evident in the demonstration of the immunobiological reaction to the invasion of an infectious agent (Widal's reaction in typhoid, Wassermann's reaction in syphilis) or in the direct observation of the causative agent (sight of the mycobacterium in sputum, or of the Klebs-Löffler baccilus in a tonsillar pseudomembrane).

SIMPLIFICATION OF ANTIMICROBIAL THERAPY

The third result of the introduction of antibiotics is the marvelous simplification of antimicrobial therapy. We have only to compare the voluminous treatises on

classic pathology written fifty years ago by famous European clinicians, describing innumerable empirical treatments of infections, with the equivalent sober chapter in a modern medical textbook explaining with great sparsity of words and naked statistics, aligned like shivering recruits, what specific drugs are to be used and in what dosage.

Therapy thus based on the use of antibiotics is becoming more and more etiological and less pathogenic. It begins with the knowledge of the clinical facts, but instead of stopping, as it did formerly, with the pathogenic link of the pathological process, it attempts quickly to reach the etiology. For any treatment founded only on pathogenesis is neither scientific nor acceptable practically, unless the etiology is known. But in such cases it is even preferable to use available antibiotics in an attempt to "focus" the group of etiologies in which the specific causal agent of the infection might be found. If after that we still do not obtain even a vague idea of the causative agent, it is preferable to accept what has been called an "etiologic purpose" to guide the clinician as the stars guide the navigator without a compass.*

FACETS OF OXYTETRACYCLINE

Among the broad-spectrum antibiotics, oxytetracycline deserves special attention for several reasons, of which the main one may be appreciated simply by reading this symposium and envisaging the gigantic horizon of its clinical indications and the honor roll of its therapeutic successes.

Unlike penicillin, oxytetracycline was discovered not by a single investigator but by a group working as a team. If in the history of medicine the discovery of certain drugs stems from the observation of Nature as a philosophical revelation of God, the discovery of this particular drug is the result of the scientific labor of a group of men for whom medical art and science were the true revelations of man.

The discovery of oxytetracycline was not one of those "famous accidents" so frequent in medical history, which, by the way, happen only to those who deserve them, to those who possess, as Sir Henry Dale has said, "natural aptitude . . . skilled curiosity . . . and mature experience," and which we can trace from Archimedes' discovery of the adulteration of gold in the royal crown to Pasteur's accidental discovery of the crystallography of the two isomeric forms of tartaric acid. On the contrary, oxytetracycline represented the final goal of carefully planned research, in which the element of chance was reduced to a minimum by putting the maximum effort into assuring the scientific precision of the project.

With oxytetracycline the term "broad spectrum" was definitely incorporated into medical terminology, and today it is spreading to other clinical fields. It has been said that the broader the spectrum of an antibacterial substance the less its specificity and the greater its toxicity, for the most powerful broad-spectrum antibiotic theoretically would be the one that was a general protoplasmic poison. But this is not

* Quite often, paradoxically, the physician cures an infectious process of indeterminate origin with antibiotics, and such an empirical cure leads *a posteriori* to the discovery of the unknown etiology; thus he acquires a knowledge which he can apply to similar cases in the future.

applicable to the broad-spectrum antibiotics used today by the physician, because their main characteristic is that the breadth of their antimicrobial spectrum is linked with a maximum reduction in their toxicity spectrum. The "toxic" horizon of an antibiotic like oxytetracycline is almost exclusively occupied by microbes that are susceptible to it and not by its human host.

Along with other broad-spectrum antibiotics, oxytetracycline has passed through the historical phases of isolation of its active principle, purification, stabilization, and determination of its atomic architecture as the key to explain its therapeutic action against given bacterial organisms.

It is interesting that in the evolution of oxytetracycline, the knowledge of its index of therapeutic activity considerably preceded knowledge of its chemical structure. But as soon as the latter was known, research workers continued to try to create variations in the molecular structure of oxytetracycline in the hope that thus they might discover a variation in its therapeutic activity.

The progress of research in this field is limited not only by the imagination of the chemist, but by the material possibility of translating his mental conceptions into chemical realities in the laboratory. Yet it is possible to predict that future investigators will explore bacterial physiology and metabolism for the purpose of synthesizing new antibiotics specifically oriented against certain bacteria, keeping in mind, however, what phase of bacterial physiology they intend to attack, what weak points of their enzyme systems they want to alter, what bacterial metabolites they plan to replace. In short, in what way they can deliver the mortal blow to bacterial development on the basis of the peculiar chemical structure of the antibiotic synthesized for such a purpose.

PERSPECTIVES OF THE SYMPOSIUM ON OXYTETRACYCLINE

Beginning with this issue, the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS will publish periodically a series of symposia presenting in terse language and clear outline the present state of our practical knowledge of antibiotics, beginning with the so-called broad-spectrum antibiotics, in this case with oxytetracycline, which since 1950 has enriched the antibiotic arsenal of the modern physician.

Under the expert direction of Dr. Merle Musselman, the facts and perspectives currently available on the application of oxytetracycline to different medical fields have been written up and harmoniously integrated into this symposium—a veritable academy on paper. Thus a marriage has been effected between concrete facts and directives that will serve to point out new therapeutic paths in antibiotic medicine.

A brief glance at the themes developed here gives us an idea of the clinical importance of this broad-spectrum antibiotic and of its transcendental significance not only in academic annals, but also in the office of the general practitioner, in the hospital, and wherever the physician is confronted with the dramatic problem of infection, which is the most urgent problem in medicine and the one that demands quick and effective action.

The papers in this symposium combine the two phases through which the study of

the effectiveness of a new therapeutic agent evolves in history. Alongside reports on isolated individual cases, so useful when one is clinically trying out a new antibiotic or an "old" one in a new group of indications, stands the evaluation of great numbers of cases presented in other articles.

The first reports represent the *individual* phase of the evaluation of a drug, in which each and every result is weighed and related to the modality of each clinical case, and the second group of reports represents the *statistical* phase in which great numbers of "depersonalized" cases are used. The integration of both phases—the first, dealing with individualized cases of medical practice, and the second with hospital statistics—culminates in the final evaluation of an antibiotic, later translated into the formation of a doctrinal and practical corpus around it, like that which already exists around oxytetracycline.

In these papers the authors attempt to serve the reader by presenting their personal findings without pretending to make of their work showcases of science. Clinical analysis is not accepted as the final word, but rather as objective information which must be evaluated in close comparison with the data provided by the patient's clinical pathology.

Attention is drawn to the simplicity with which the cases and their treatment are presented in this symposium. The practical, even naturalistic, focus of these articles confirms what Darwin said in the final years of his life: that the naturalist who has merely counted the leaves of a plant has done more to fulfill his duty to study Nature than the author of purely theoretical disquisitions. From this point of view, it is of the utmost importance that we continue to compile "common" clinical histories, those "ordinary" cases which are the small change of medicine, but which, as with all small change, can be accumulated into a treasure of clinical knowledge.

ANTIBIOTICS AND THE ART OF HEALING

Broad-spectrum antibiotics, such as oxytetracycline, have not only widened the therapeutic horizon of the physician, they have also broadened his philosophic conception of the ends, means, and resouces of clinical medicine. If the second half of the nineteenth century was fertile in doctrinal elaborations, the first half of our century has witnessed the reaping of a magnificent therapeutic crop.

Parallel with the progress of medicine as a science, we have witnessed the rise of the art of healing per se. And healing is the most important goal not only for the patient, but also for the physician. The growing splendor of experimental disciplines should not make us forget that experimentation is only an accessory of the empirical and humble, but all-important, art of healing. Only when the physician keeps before him the prospects of curing his patient does he achieve true greatness for himself and the medical profession. Paraphrasing the classical Castilian poet, all medical knowledge, whatever course it may follow, must, like all rivers, finally flow into the vast sea of healing.

Viewed from this angle, broad-spectrum antibiotics represent a supreme contribution to the art of healing, not as an easy way of by-passing a doubtful clinical situation, but as an incentive to refine diagnosis and hasten the cure of infectious diseases.

For infection is perhaps the most dramatic of man's pathological contingencies. It mobilizes the entire organism in response to the alarm warnings from those organic "Pentagons" which comprise the pituitary-adrenal axis and the hypothalamic centers. The entire organism declares war on the invading bacteria and marshals all its resources, from the most humble humoral defenses to the supreme neuroendocrinal centers governing the organism. The danger is universal in any infection, and the response of the human being is also universal. Antibiotic therapy, even if specific, enjoys universality in the sense that it spreads throughout the body until it enters into battle with the bacterial invaders—wherever they may be—thus also responding to that etiological aim discussed earlier.

Antibiotic therapy is an etiological and integral therapy, specific in its objectives and integral in its conception, as proved by the recent introduction of certain compounds combining vitamins and antibiotics, which help to fight stress in an invectious patient and to strengthen his defenses; in one word, modern therapeutic weapons are being used towards the classical goal of treating the *whole* patient.

Thus, we see a restoration of the concept that the *whole* patient should be treated, including his nutrition and his psyche, even in the case of infections. Let us not forget that the word *holy* has the same etiological root (*hal*) as the words *health* and *whole*. If Medicine wishes to recover its philosophical holiness, which is the same as saying its historical dignity, it must treat the *whole* patient. Medicine is *una et indivisibilis*.

Symposia on New Facts and Perspectives of Broad-Spectrum Antibiotic Therapy

I. OXYTETRACYCLINE

Guest Editor—Merle M. Musselman, M.D.

Part 1*

INTRODUCTION

Oxytetracycline is a "utility member" of the antibiotic team in that it is effective against most of the clinically important pathogens. It may be administered in many forms, is usually well-tolerated, and is effective in a great variety of diseases but, like any fine tool, it should not be used indiscriminately. We should make it a rule to identify the responsible organisms and determine their sensitivity to the various antibiotics with the start of treatment. However, as expressed by Spink (1953), under uncertain circumstances when it is impossible to acquire precise laboratory information regarding the etiologic agent responsible for an infection, one may turn to a broad-spectrum antibiotic which affects gram-positive and gram-negative bacteria as well as the rickettsiae and even some of the larger viruses.

Oxytetracycline has little if any toxicity in clinical use because of the wide difference between therapeutic and toxic doses. The few side effects are rather well limited to the gastrointestinal tract. As oxytetracycline is used now, these are usually of little consequence. But we should be alert for its possible side effects and be familiar with methods to minimize these side effects if they appear.

Oxytetracycline is effective in diseases encountered in all the divisions of medicine and surgery. The contributors to this Symposium have described the use of oxytetracycline in the more important diseases in their special fields. While they have described the principles for employing oxytetracycline including routes of administration and dosage, they have emphasized the principles which they follow in treating the diseases discussed.

M. M. Musselman

* Part 2 will appear in the April, 1955, issue of International Record of Medicine and General Practice Clinics.

Antimicrobial Activity, Pharmacology, Chemistry, and Clinical Uses of Oxytetracycline

M. M. Musselman, M.D., and H. L. Davis, Ph.D.

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OMAHA, NEBRASKA

Since its discovery in 1950,[22] oxytetracycline* has been used successfully for the treatment of a wide variety of infectious diseases because of its wide range of activity against bacteria, rickettsiae, large viruses, and even some Protozoa and Metazoa. It may be administered orally or parenterally and is widely distributed through the body fluids, tissues, and secretions in effective concentrations. Minimal toxicity has been demonstrated in the dosages used and serious reactions have been rare. Side effects have been limited to the gastrointestinal tract for the most part and have been of little consequence. Because of its chemical structure it is freely soluble in the body and can be stored for long periods of time without loss in activity. The variety of preparations of oxytetracycline for oral, parenteral, and topical use allow one to cope with all conceivable problems of treatment.

ANTIMICROBIAL ACTIVITY

Oxytetracycline inhibits the growth of a great variety of pathogens in a concentration of 1 to 8 μg./ml. So great is the variety of aerobic and anaerobic, gram-positive and gram-negative bacteria and other organisms against which it is effective, that it is simpler to list those which are usually resistant to it. Two common pathogens, *Pseudomonas aeruginosa* and *Proteus vulgaris* are resistant to its antibacterial activity.[22, 75, 77] This resistance to antibiotic treatment may be reduced by combining neomycin with the administration of oxytetracycline. It is also inactive against yeast-like organisms.[75, 77]

Finlay and his associates[22] initially reported that oxytetracycline in concentrations of 5 μg./ml. or less inhibited strains of *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella typhosa*, *S. paratyphi*, *S. schottmülleri*, *Shigella paradysenteriae*, *Bacillus subtilis*, *Staphylococcus albus*, *S. aureus*, and *Brucella bronchisepticae*. *Ps. aeruginosa* and *Proteus sp.* were resistant to concentrations of 100 μg./ml. and over 1,000 μg./ml., respectively. Welch and his group[77] found a wide range of activity against many species, both gram-positive and gram-negative. Thirty seven of 54 different bacterial strains were sensitive to a concentration of 1 μg./ml. or less and five strains were sensitive to from 1 to 5 μg./ml. Ten strains were sensitive to a concentration greater than 5 μg./ml. The drug was especially active against the clostridia and saprophytic mycobacteria. It was inactive against *P. vulgaris* and had little or no effect on fungi. It was apparent that oxytetracycline possessed a bacteriostatic rather than a bactericidal effect.

*The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

Hobby and her group[23] reported that oxytetracycline was active in vitro and in vivo against a wide variety of pathogenic organisms belonging to the bacterial, spirochetal, and rickettsial groups. They also cited evidence that it was active against certain of the larger viruses and against *Endamoeba histolytica*. They reported that of 109 strains tested, 56 per cent were sensitive to less than 1 μg./ml. and 83 per cent were sensitive to less than 5 μg./ml. Only *P. vulgaris* was uniformly resistant to its action.

Groups headed by Bauer,[4] Rose,[62] Schoenbach,[64] Smadel,[66] and Snyder[67] reported an anti-rickettsial effect of oxytetracycline in experimental or in clinical infections.

Although little anti-viral effect was demonstrated experimentally,[22, 39, 56] it was considered of some benefit clinically.[21, 41] It has been found effective against primary atypical pneumonia and the larger viruses of granuloma inguinale and lymphogranuloma venereum.

The staphylococci. *Staph. aureus* and some strains of *Staph. albus* were reported susceptible to oxytetracycline in vitro.[13, 22, 23, 77] Gocke and his associates[23] found a wide range of sensitivity to oxytetracycline for *Staph. aureus*. Of 39 strains, 12 were susceptible but more than one half grew profusely in 800 μg./ml. of oxytetracycline. All but two of the strains were hemolytic and coagulase positive.

Despite the development of resistance by the staphylococci which has been shown to occur as discussed later in this section under "Resistance and Cross Resistance," Pulaski, Artz, and Reiss[65] found only 11 per cent of 228 strains of staphylococci resistant to oxytetracycline in 1952. Of 44 penicillin-resistant strains, 86 per cent were sensitive to oxytetracycline. Eisenberg and his associates,[15] in 1953, found 73 per cent of 255 strains of *Micrococcus pyogenes* var. *aureus* susceptible to oxytetracycline. Seventy-eight per cent of 135 strains of *M. pyogenes* var. *albus* were susceptible to oxytetracycline.

The streptococci. The streptococci including *Streptococcus faecalis* have been found to be susceptible to oxytetracycline.[22, 23] Gocke and his colleagues[23] found group A hemolytic streptococcus and pneumococci the most sensitive of the gram-positive cocci. He found the other hemolytic streptococci and *Streptococcus viridans* also susceptible.

The pneumococci. Oxytetracycline has been shown to be effective against *Diplococcus pneumoniae*.[23, 23]

The neisseria group. *Neisseria catarrhalis*, *Neisseria meningitidis*, and *Neisseria gonorrhoeae* have been shown to be susceptible to oxytetracycline.[23] Gocke[23] found 28 strains of *N. gonorrhoeae* highly susceptible.

The enteric organisms. Finlay and his associates[22] found that oxytetracycline in a concentration of 5 μg./ml. or less inhibited strains of *A. aerogenes*, *Esch. coli*, *S. typhosa*, *S. paratyphi*, *S. schmottmülleri*, and *S. paradysenteria*. *Ps. aeruginosa* and *Proteus sp.* were resistant to concentrations of 100 μg./ml. and over 1,000 μg./ml., respectively. Gocke and his group[23] found the salmonellas and shigellas to be the most sensitive of the gram-negative bacilli. The order of increasing resistance of the remaining enteric organisms tested was *Esch. coli*, *A. aerogenes*, *Ps. aeruginosa*, and *P. vulgaris*. Others[1, 23, 77] made similar observations as to the organisms sensitive to oxytetracycline and found *Ps. aeruginosa* and *P. vulgaris* to be resistant. In addition

oxytetracycline was reported to be effective against the gram-positive cocci and the anaerobic bacilli,[1] and, more specifically, against Bacteroides,[14] *Str. faecalis*, and clostridia. Hammond and Miller[26] found that the administration of oxytetracycline protected irradiated mice against the septicemia from intestinal bacteria which occurs the second week after irradiation except when it was caused by oxytetracycline-insensitive bacteria. The most common of these was Pseudomonas. In 1953, Eisenberg and his associates[15] reported finding 82 per cent of 150 strains of alpha hemolytic streptococci and 60 per cent of beta hemolytic streptococci susceptible to oxytetracycline. Pulaski and his co-workers[55] found over half the organisms of the coli-aerogenes group which they encountered sensitive to oxytetracycline. Although *P. vulgaris* and *Ps. aeruginosa* were generally resistant they found a few strains sensitive.

Herrell and his associates[29] found that strains of *Esch. coli* and *A. aerogenes* made resistant to oxytetracycline had an increased resistance to chlortetracycline and chloramphenicol but not to streptomycin. Strains made resistant to streptomycin were not resistant to the others. In fact, they found an increased sensitivity in either case for which reason they suggested the value of combining one of the broad-spectrum antibiotics with streptomycin.

In a study of enteric organisms encountered in urinary tract infections, Rhoads and his group[61] reported the following results. Forty-six per cent of the strains of *Esch. coli* tested were sensitive to oxytetracycline in a concentration of 0 to 25 μg./ml. but 73 per cent were sensitive to a combination of equal parts of oxytetracycline and neomycin in a total concentration of 0 to 25 μg./ml. Forty per cent of the strains of *Str. faecalis* were sensitive to 0 to 25 μg./ml. of oxytetracycline but 64 per cent were sensitive to a combination of oxytetracycline and streptomycin. Twenty-nine per cent of the strains of *A. aerogenes* were sensitive to oxytetracycline in the same concentration but 57 per cent were sensitive to a combination of oxytetracycline and neomycin and 71 per cent were sensitive to a combination of oxytetracycline and chloramphenicol. They found only 16 per cent of *Ps. aeruginosa* sensitive to 0 to 25 μg./ml. of oxytetracycline but 63 per cent were sensitive to a combination of oxytetracycline and neomycin, 44 per cent to oxytetracycline and chloramphenicol, and 41 per cent to oxytetracycline and Gantrisin. In all instances, the combination of drugs was more effective than either alone. They point out that these results were not entirely in accord with the observations of Jawetz that antibiotics in group I (penicillin, streptomycin, bacitracin, neomycin) are frequently synergistic and never antagonistic; members of group II (oxytetracycline, chlortetracycline, chloramphenicol) are neither synergistic or antagonistic but additive, and the bactericidal effect of a member of group I may be inhibited by a member of group II.

Oxytetracycline alters the flora of the bowel when given orally. It is generally agreed that the growth of *Esch. coli*, the anaerobic bacilli, and *A. aerogenes* is suppressed while there is an increase in the numbers of Proteus.[1, 5, 14, 29, 30, 44] Some workers have reported little change or a decrease in enterococci.[1, 29, 30, 44] In contrast to these findings and those of Eisenberg's group[15] that most strains of alpha hemolytic enterococci and beta hemolytic enterococci are susceptible to oxytetracycline, Spaulding,[65] Broitman,[5] and their fellow workers have found an increase

in the total count and the numbers of enterococci as well as Proteus after the oral administration of oxytetracycline. Broitman and his associates observed that patients receiving the amphoteric form exhibited a lower number of enterococci and total aerobes per gram of feces than those receiving the hydrochloride. Both Spaulding's group and Broitman's group emphasized that such a disturbance of the normal flora of the bowel may argue against "sterilization" of the bowel with oxytetracycline before operations on the bowel, for the escape of such organisms may be more prone to cause infection than the original flora. Yeasts are very resistant to oxytetracycline and when present in the bowel they increase with the oral administration of oxytetracycline.[14]

The pseudomembranous enterocolitis which has occasionally occurred after the oral administration of the antibiotics is discussed later in the section "Toxicity" under "Pharmacology."

Combining neomycin with oxytetracycline in the preoperative preparation of the bowel may reduce the complications from alteration of the flora of the bowel.[7, 15] McKittrick[15] strongly questions the philosophy of preoperative preparation of the bowel with antibiotics. He believes there is no evidence that healing occurs more promptly or that such "sterilization" protects against disruption of the suture line caused by poor technique. This attitude is supported by the experimental work of McCorkle and his group.[17] Both agree that emphasis belongs on protection through proper technique. This emphasizes the statement of Fleming that "antibiotics simply attack the bacteria—the surgeon must treat the patient."

Miscellaneous bacilli. *Hemophilus influenzae*, *H. pertussis*, and *K. pneumoniae* are sensitive to oxytetracycline.[6, 22, 28, 33] Oxytetracycline has been found clinically effective against *Hemophilus ducreyi* and *Bacillus anthracis*.

The diphtheria bacillus. *Corynebacterium diphtheriae* is highly susceptible to oxytetracycline.[23, 33]

The clostridia. Oxytetracycline was found to be quite active against clostridia in vitro[6, 33, 77] and was shown to be effective against experimental infections with *Clostridium tetani* and *Clostridium septicum* in mice.[6, 71] *Clostridium welchii*, *Clostridium botulinum*, *Cl. sporogenes*, *Cl. tetani*, and *Clostridium perfringens* are susceptible in vitro. Taylor and Novak[72] found that experimental clostridial infections in mice produced by detoxified spores of *Cl. septicum*, *Clostridium bifermentans*, *Clostridium histolyticum*, and *Clostridium novyi* were most effectively controlled, prophylactically, by the local administration of oxytetracycline. Only antitoxin was protective against infection with *Cl. perfringens*. A detailed study of the action of oxytetracycline in *Cl. septicum* infections indicated the superiority of local administration over systemic and the value of delayed and multiple doses in control.

The mycobacteria. Oxytetracycline has been shown to be quite active against the saprophytic mycobacteria and *Mycobacterium tuberculosis* in vitro.[33, 75, 77] Steenken and Wolinsky[70] noted tuberculostatic activity of oxytetracycline in vitro and in guinea pigs and mice. It was more effective than *p*-aminosalicylic acid and tibione but less effective than viomycin and streptomycin. The minimal inhibitory concentration was 5 to 10 μg./ml. No resistance developed after five transfers.

Miller and his group[47] treated 70 patients with active pulmonary tuberculosis for 120 days with 5 Gm. of oxytetracycline per day and 2 Gm. of streptomycin every three days. Of 66 patients who completed a full course of treatment, 97 per cent showed x-ray improvement; 50 per cent showed marked or moderate improvement. At the end of treatment 77 per cent were bacteriologically negative for *M. tuberculosis*. By National Tuberculosis Association standards, 60 per cent had converted their sputum by the end of a 60 day follow-up period. In each of 25 patients who had a positive culture for *M. tuberculosis*, the organisms were susceptible to both streptomycin and oxytetracycline.

Oxytetracycline is now recommended for use in conjunction with streptomycin to delay emergence of microbial resistance to streptomycin in patients unable to tolerate, or infected with organisms resistant to, *p*-aminosalicylic acid or isoniazid.

The actinomyces. Oxytetracycline is effective against actinomyces in the treatment of actinomycosis.[48]

The brucella group. The brucella are susceptible to oxytetracycline in vitro.[22, 33] Knight[42] demonstrated that oxytetracycline controls the acute manifestations of brucellosis. Herrell and his associates[20] found the brucella most sensitive to oxytetracycline in vitro. In experimental infections in mice, *Br. suis* was considerably suppressed by oxytetracycline. However, not all of the organisms were eliminated from the spleens of the mice. Its effect was considerably augmented by using dihydrostreptomycin in combination with it.

The pasteurella group. Oxytetracycline has been shown to be effective against *Pasteurella pestis* and *Pasteurella tularensis* in vitro[33] and in experimental infections with *Past. tularensis* in mice.[4] It is clinically effective in tularemia.

The spirochetes. Oxytetracycline has been reported to be effective in spirochetal diseases[28, 33] and its use in syphilis, yaws, pinta, bejel, rat bite fever, relapsing fever, Weil's disease, and tropical ulcer is discussed in this symposium by Frye, Loughlin, and Robinson.

The rickettsial group. Oxytetracycline was reported as effective against the rickettsiae.[33] Snyder and his co-workers[67] found it suppressed the multiplication of *Rickettsia prowazekii* and *Rickettsia rickettsii* in chick embryos. It protected mice against a severe challenge with *Rickettsia tsutsugamushi*. Rose[62] found a definite effect against *Rickettsia akari* in chick embryos and mice. He also found it effective in the treatment of 4 patients with rickettsialpox. Smadel, Jackson, and Ley[66] found oxytetracycline effective against *R. tsutsugamushi*, *R. rickettsii*, and *Rickettsia burneti* in chick embryos. They also found it clinically effective in 6 patients with naturally acquired scrub typhus (*R. tsutsugamushi*). Bauer and his associates[4] reported a rickettsiostatic effect of oxytetracycline against *R. rickettsii* in chick embryos. They also found it effective in 2 patients with Rocky Mountain spotted fever (*R. rickettsii*) and in 1 patient with murine typhus (*Rickettsia mooseri*). Schoenbach, Bryer, and Long[61] also reported the use of oxytetracycline in the successful management of 2 patients with Rocky Mountain spotted fever.

The filtrable viruses. Quilligan and his fellow workers[56] found that oxytetracycline suppressed the multiplication of influenza virus in experimental infections in chick embryos only if the toxic level of the drug was approached and if the material

was given before the virus. They could demonstrate no effect on the course of type A influenza virus infection in mice, on growth of strains of herpes simplex virus in chick embryos or mice, or on the multiplication of a strain of rabies virus in mice. Kass, Barnes, and Finland[35] could demonstrate no effect of oxytetracycline in experimental infection with influenza A virus in chick embryos and mice. Although 4 of 5 patients with influenza became afebrile and asymptomatic promptly after its use, they concluded that it could not be interpreted as indicating any beneficial effect of the oxytetracycline.

On the other hand, Finland and others[21] considered oxytetracycline clinically effective in 7 of 8 patients with influenza and 5 of 6 patients with pertussis. Kneeland and Melcher[41] found that it produced a prompt and favorable effect in all of 10 patients with primary atypical virus pneumonia. It was reported to be active against certain of the larger viruses[33] and its effectiveness in the treatment of lymphopathia venereum is discussed in this symposium by Herrell and Loughlin and Mullin.

Miscellaneous. Oxytetracycline is effective in the treatment of granuloma inguinale, psittacosis, and bartonellosis or Carrion's disease. It is also effective against enterobiasis or pinworm infestations.[9, 39] Its effectiveness in amebiasis is discussed in this symposium by Frye. Oxytetracycline has not been shown to be effective against the other intestinal parasites. Greene[24] found oxytetracycline clinically effective in 21 patients with *Trichomonas vaginalis*.

MODE OF ACTION

Antiseptics appear to function in various ways—by coagulating protoplasm of bacteria, by modifying cell membrane permeability, or by interfering with one or more enzymatic processes on which the organism depends.[12] Poisoning of essential enzymes appears most general for antibiotics. Hobby[32] has summarized several reports. Interference with protein metabolism, with phosphorylation, with oxidation of glutamate, with oxygen consumption, and general respiration were among the effects demonstrated for oxytetracycline and analogous compounds.

It has been shown that the action of antiseptics may be reversed by neutralizers which release apparently killed organisms from the effect of an antiseptic to grow in cultures previously "sterilized" by the antiseptic. For instance, the effect of the mercurial antiseptics may be reversed by a neutralizer, such as glutathione, so that bacteria are free to be grown from a culture in which previously there was no growth. In order to demonstrate that organisms have been truly killed by an antimicrobial substance, it is necessary to apply a neutralizer to determine if the effect of the substance was inhibitory or bactericidal. No effective neutralizers for oxytetracycline are known, so the distinction between inhibition and bactericidal effects cannot be made precisely.[12]

It is well to bear the above in mind in considering the mode of action of oxytetracycline. According to classic concepts, oxytetracycline is bacteriostatic rather than bactericidal in nature[31, 37] in that growth occurs with dilution of the bacteria-oxytetracycline system. It exerts a bactericidal effect when the ratio of its concentration to the initial number of organisms is high. Its bactericidal concentration is

more than 10 times its minimum inhibitory concentration.[6] Oxytetracycline is similar to the sulfonamides in that, under conditions suitable for bacteriostasis, antimicrobial action is apparent only after a prolonged lag period.[23] It differs from the sulfonamides, however, in its ability to produce a bactericidal effect under appropriate conditions.

Oxytetracycline has an inhibitory effect on the synthesis of cell protein[55] and an inhibitory action on nucleic acid metabolism[45] in bacteria. Because the activity of oxytetracycline was demonstrated to be depressed by the addition of salts of iron, magnesium, and manganese, it has been suggested that the drug may combine with divalent metallic cations essential for enzymatic action.[71] Oxytetracycline may[45] or may not[56] inhibit phosphorylation.

Benigno and his associates[5] demonstrated that oxytetracycline decreased metabolism, slackened growth, inhibited division, and caused a decline in the numbers of organisms while not modifying the phosphorus uptake.

RESISTANCE AND CROSS RESISTANCE

According to Bryson and Demerec,[10] the development of resistance to oxytetracycline follows the same pattern as that for penicillin, chlortetracycline, chloramphenicol, and neomycin, occurring gradually as a result of multiple genetic mutations. They predicted that the clinical use of oxytetracycline should not lead to the development of resistant strains as frequently as with streptomycin, which often produces spontaneous resistance by a single genetic change. Strains of *Esch. coli*, *A. aerogenes* and *Str. faecalis* made resistant to oxytetracycline, chlortetracycline, or chloramphenicol become resistant to the others but not to streptomycin.[29] Strains resistant to streptomycin were not resistant to the others.

Oxytetracycline was active against most strains of micrococci when first introduced. The report by Gocke's group[24] that over half of 39 strains of *Staph. aureus* grew profusely in a concentration of oxytetracycline of 800 μg./ml. was an exception. Most observers reported few or no resistant strains. But according to subsequent reports the emergence of such resistant strains has been increasing. In 1953, Spink[69] reported that approximately 40 per cent of strains isolated at his hospitals were resistant. Dearing and Heilman[13] reviewed the development of resistant strains of micrococci from none in 1950, to 9 per cent early in 1951, 36 per cent later in 1951, and 45 per cent in 1953. In a special study of 44 patients with pseudomembranous enterocolitis in 1953, they found 38 of 41 strains of *M. pyogenes* isolated resistant to oxytetracycline, chlortetracycline, and streptomycin. Kirby and Ahern[40] found that in the period from August, 1951, to May, 1952, 42 per cent of micrococci obtained from patients were resistant to oxytetracycline. A year later, from January to April, 1953, 61 per cent were found to be resistant. In most instances the infections were acquired in the hospital.

In contrast to the above reports, Pulaski, Artz, and Reiss[55] found only 11 per cent of 228 strains of micrococci resistant to oxytetracycline in 1952. Eisenberg, Flippin, and O'Loughlin,[18] in 1953, found 73 per cent of 255 strains of *M. pyogenes* var. *aureus* and 78 per cent of 135 strains of *M. pyogenes* var. *albus* susceptible to oxytetracycline.

Welch[76] has reviewed the development of resistance by micrococci to all anti-

biotics. He describes the reported increase in numbers of micrococci resistant to oxytetracycline. The increase of resistant organisms has been greater in hospitalized than in non-hospitalized populations. He believes the increase in resistance has been magnified by studies of infections in hospitals. These result largely from cross infections and the high incidence of resistant organisms does not reflect the actual situation. Cross infections apparently occur both through carriers of resistant micrococci among hospital personnel and from patient to patient.

Welch[76] reports that a higher proportion of the strains isolated from the feces were resistant to oxytetracycline than were strains isolated from other sources. Strains of micrococci showed a close correlation between resistance to chlortetracycline and oxytetracycline. Strains resistant to chlortetracycline and oxytetracycline were all resistant to penicillin, although strains resistant to penicillin were not necessarily resistant to the other two drugs. Chloramphenicol was more effective against micrococci than chlortetracycline or oxytetracycline and fewer strains became resistant to it. Rantz and Randall[57] found no combination of group I antibiotics (synergistic—penicillin, streptomycin, bacitracin, neomycin) and group II antibiotics (additive—oxytetracycline, chlortetracycline, chloramphenicol) effective in vitro against highly penicillin-resistant, streptomycin-resistant, and oxytetracycline-resistant strains of *Staph. aureus*.

As stated by Welch,[76] in the event of the development of resistance to oxytetracycline by micrococci, carbomycin, erythromycin, bacitracin, and chloramphenicol are available. Although sensitivity studies are desirable, time may not permit such studies. He suggests that since most hospital infections are cross infections, the sensitivity of the organisms peculiar to a hospital might be established by routine studies of the organisms in the stools, noses, and throats of patients. This information would be helpful should a patient develop a fulminating micrococcic enteritis.

PHARMACOLOGY

Clinically effective serum levels of oxytetracycline are obtained when it is given orally, intravenously, subcutaneously, intramuscularly, or intraperitoneally. Oxytetracycline is rapidly absorbed from the gastrointestinal tract, becomes widely distributed in the tissues and fluids of the body, and is excreted in the bile, stool, and urine. After a single oral dose of 1 Gm. it can be found in the serum after one to two hours. It reaches its maximum concentration of about 3 μg. in four to six hours after which the level falls off but some activity persists for as long as 24 hours. The levels obtained with doses of 0.5 Gm., 0.75 Gm., and 1.0 Gm. are roughly proportional but the increase obtained with doses above 1.0 Gm. is less than proportional. Apparently between the lower and higher doses a point of optimum absorption is reached above which excess drug is lost in the feces. In any case, a large amount of oxytetracycline is unabsorbed and excreted in the feces. In patients receiving about 1.0 Gm. every six hours, a concentration of 2.5 μg./ml. may be found in the stool.[59, 64, 75, 77]

When oxytetracycline is given in multiple doses every six hours, there is a cumulative effect in the serum levels obtained. With dosages of 0.25 Gm., 0.5 Gm., or

1.0 Gm. every six hours, minimal sustained levels of about 1.0 μg., 2.0 μg., and 4.0 μg./ml., respectively are obtained.[39, 64, 76, 77]

There is evidence that a greater proportion of oxytetracycline is absorbed from the stomach, less from the intestine.[11] Also, it was shown that oxytetracycline is removed from the blood by the liver, concentrated by the liver, and excreted in the bile after which it is reabsorbed from the intestine. Because of this entero-biliary circuit a small amount of oxytetracycline can persist in the blood for a long time.

Aluminum gel interferes with the absorption of oxytetracycline from the gastrointestinal tract but food does not.[46] Neither does cation exchange resin interfere with its absorption.[75] Oxytetracycline is not absorbed from the rectum so cannot be given by proctoclysis or retention enema.[35, 39]

Oxytetracycline may be given intravenously. After intravenous administration a high serum concentration is rapidly attained and maintained for about 12 hours. Effective minimal serum levels are maintained with a dosage of from 0.5 Gm. to 1.0 Gm. every 12 hours. The efficacy, safety, and practicability of the intravenous administration of oxytetracycline has been established by extensive clinical use.

Farley and Konieczny[20] and Kagan's group[37] obtained clinically significant blood levels of oxytetracycline in children by giving it subcutaneously. They used the preparation for intravenous use in concentrations up to 5 mg./ml. They recommend using a concentration of 1 mg./ml. and a dosage of 10 to 25 mg./Kg. of body weight every 8 to 12 hours.

A preparation of oxytetracycline is available for intramuscular use. It is well tolerated in concentrations up to 100 mg./ml. and has been shown to be free from untoward reactions and effective by extensive use.[7, 49] Clinically significant serum levels can be maintained by a dosage of 100 mg. every eight hours. Doses above 100 mg. do not increase serum levels proportionately. Because of the presence of procaine in the preparation, patients suspected of being sensitive to procaine for any reason should be skin tested before it is administered. Brannick's group encountered a few instances of micrococcal ileocolitis in patients receiving intramuscular oxytetracycline. They had hoped this complication might not occur with the administration of the drug by the parenteral route. Perhaps it resulted from the excretion of a significant amount of oxytetracycline into the bowel by way of the bile. The fact that it did occur is interesting. However, since three fourths of their patients were also being given dihydrostreptomycin and since the relationship between antibiotic therapy and micrococcal enterocolitis is not clear, no conclusion can be drawn from it.

Schatten and Abbott[63] reported the use of oxytetracycline intraperitoneally in experimental peritonitis in dogs. They found it effective in prolonging life and reducing mortality. The results were better than in a group of dogs treated with intravenous oxytetracycline. In the dosage used (400 mg. every 12 hours in 7 to 16 Kg. dogs), high spiking levels were found in the peritoneal fluid and high sustained levels in the serum. They also used oxytetracycline intraperitoneally in 3 patients with peritonitis with good results and with no untoward reactions.

Oxytetracycline diffuses readily through most bodily tissues to become widely distributed throughout the body.[76] When therapeutically effective levels are present

in the blood, oxytetracycline diffuses into the pleural fluid,[29, 30] and ascitic fluid.[55] It diffuses readily through the placenta[29, 30] and reaches levels in the fetal serum about one fourth that of the maternal serum.[64]

Oxytetracycline does not appear to diffuse well into the cerebrospinal fluid when therapeutically effective serum levels are maintained.[29, 30, 64] Diffusion into the cerebrospinal fluid appears to be enhanced by inflammation of the meninges. Pulaski's group[65] found 3.84 μg./ml. of oxytetracycline in the spinal fluid of a patient with a streptococcal meningitis receiving 1 Gm. of oxytetracycline intravenously every 12 hours.

Welch[78] found that after a single oral dose of 0.5 Gm./Kg. in rabbits, the concentration of oxytetracycline in the liver and kidney was higher than that in the blood. The concentration in the brain, heart, and skin was several times that in the blood. The concentration in the spleen and lungs was even higher. Helander and Bottiger[27] by a technique of fluorescent microscopy found oxytetracycline concentrated in the reticulo-endothelial system (bone marrow, spleen, lymph glands) and in the liver and kidney. They demonstrated none in the connective tissue, cartilage, bone, walls of vessels, muscle, brain, peripheral nerves, or lungs.

Fairly large amounts of oxytetracycline, estimated at 10 to 35 per cent of that administered, are excreted in the urine.[29, 30, 75, 77] It may be detected in the urine within one-half hour after oral administration.[61] In patients with impaired renal function, relatively small doses given parenterally may produce high serum levels.[3] Oxytetracycline is concentrated in the hepatic system and excreted in the bile.[11, 29, 30, 75, 77] When given orally, a great deal is not absorbed and as much as 2.5 μg./ml. may be excreted in the feces.[29, 30, 75, 77]

TOXICITY

Finlay and his colleagues[22] reported that oxytetracycline showed a low degree of toxicity in animals. The intravenous LD_0 for oxytetracycline hydrochloride is equivalent to 103 mg./Kg. of the amphoteric compound of body weight in mice; the LD_{50} is equivalent to 192 mg./Kg. P'An's group[52] found a similar LD_{50} and an approximate ratio of intravenous to subcutaneous to oral LD_{50} of oxytetracycline hydrochloride in mice of 1:4.6:37.6. Death occurred from respiratory failure preceded by excitation, tremors, rigidity, convulsions, prostration, unconsciousness, and flaccid paralysis. Oral doses of 75 to 465 mg./Kg. for as long as eight weeks were tolerated in dogs without evidence of toxicity. Dogs tolerated oxytetracycline hydrochloride given intramuscularly in a dosage of 50 and 100 mg./Kg. per day for over 90 days.

Schoenbach, Bryer, and Long[64] found the intravenous LD_{50} of oxytetracycline hydrochloride in mice was greater than 175 mg./Kg. of body weight. Death was preceded by symptoms of central nervous system involvement similar to those observed by P'An. Death apparently resulted from respiratory arrest. They found the LD_{50} after subcutaneous administration was about 600 mg./Kg. for the hydrochloride. Both P'An's group and Schoenbach and his associates found the sodium salt was less well tolerated than the hydrochloride. Daily subcutaneous injection

of as much as 200 mg./Kg. of the hydrochloride for two weeks in rats gave no evidence of renal damage or other abnormality. The administration of 200 mg./Kg. of the sodium salt for two weeks resulted in evidence of renal toxicity. The animals lost 26 per cent of their body weight. The daily volume of urine increased two to six times and the specific gravity was reduced to 1.012. Casts and epithelial cells appeared without albuminuria. At autopsy, the thymus was atrophic without histologic change in the adrenal. The renal tubules were dilated with flattening of the tubular epithelium and denudation of the tubules of cells in some areas. Mice tolerated 200 mg./Kg. of the hydrochloride by gavage daily for eight days without deleterious effect except for a mucoid diarrhea which appeared during the first two days. This disappeared during the subsequent three days.

Nelson and Radomski[50] gave oxytetracycline to 8 dogs in a dosage of 250 mg./Kg. of body weight per day for 99 days. All the dogs survived and maintained their weight. No abnormalities were demonstrated in the peripheral blood, bone marrow, or viscera.

Because they had observed a shocklike state terminating in death in a small group of seriously ill patients after the parenteral administration of oxytetracycline, Sedwitz, Bateman, and Klopp[65] gave a group of dogs oxytetracycline intravenously in a dosage of 25 mg. to 220 mg./Kg. of body weight per day until they died. One dog died of respiratory failure 30 minutes after a single dose of 220 mg./Kg. The other 6 dogs lived for from two to seven days during which time they showed progressive azotemia, anorexia, lethargy, and weight loss. Serum levels of oxytetracycline prior to death ranged from about 10 μg. to over 250 μg./ml. There was a marked azotemia prior to death. No remarkable abnormalities were demonstrated grossly or microscopically at autopsy. They concluded that the increase in nonprotein nitrogen resulted from increased tissue breakdown, impaired renal or hepatic function, or a combination of all three, and that death resulted when the rate of administration of the drug exceeded the rate of excretion and detoxification. Later, Bateman, Klopp, and Samson[3] reported finding that a relatively small dose of antibiotic given parenterally may produce a high serum level in patients with impaired renal function. The azotemia which follows results from the increased tissue catabolism caused by the high concentration of the antibiotic in the serum. They believed it was the effect of the mounting level of antibiotic in the serum on the respiratory center or other vital tissues which kills and not the azotemia.

One type of blood dyscrasia or another has been reported in 41 patients receiving oxytetracycline.[78] This was about one-third the number reported in conjunction with the use of chloramphenicol and about the same as with chlortetracycline. The occurrence of these cases of blood dyscrasia cannot be directly attributed to the drug for their development may have been idiopathic, secondary to the primary disease or caused by exposure to other drugs or chemicals. During the period covered by the report about 500 cases of idiopathic blood dyscrasia and about 500 cases of blood dyscrasia associated with exposure to drugs or chemicals other than antibiotics were reported. In only 10 of the 41 patients was it stated that oyxtetracycline was the only drug administered. However, the possibility of the development of a blood dyscrasia during antibiotic therapy must be borne in mind.

No other toxic effects have been reported.

Although oxytetracycline has no toxic effect on liver or kidney, it may be deleterious in patients with reduced renal function. It apparently causes azotemia by increasing tissue catabolism and somewhat dangerously high serum levels may result from failure to excrete the drug.[3]

We know of only one serious allergic reaction following the administration of oxytetracycline. Johnston and Cazort[38] reported the development of severe serum sickness with cyanosis in a 10 year old girl two days after oxytetracycline was started orally for the treatment of an upper respiratory infection. The girl had been treated with oxytetracycline ointment for an ear infection one year before. She recovered with symptomatic treatment. The serum sickness may have been an allergic response to oxytetracycline but the evidence is not clear-cut that it was.

Side effects have been observed with the use of oxytetracycline. For the most part these have consisted of disturbances of the gastrointestinal tract and are more unpleasant than serious. Schoenbach, Bryer, and Long[64] reported an incidence of nausea and vomiting or diarrhea in about half of 36 patients receiving the drug but they were using large doses. They described some patients tolerating as much as 4 Gm. per day, for periods as long as two weeks without any adverse symptoms. In other patients symptoms passed with continued administration of the medicine. They reported one instance of a skin rash apparently developing as a result of treatment with oxytetracycline. Finland and his group[21] reported a similar experience.

In contrast to the above reports, Miller and his group[47] reported that of 70 patients given 5 Gm. of oxytetracycline orally per day for 120 days, 66 tolerated it with a minimum of difficulty. The remaining 4 were able to continue the medicine in reduced dosage. None exhibited toxic manifestations. Two thirds had gastrointestinal side effects but a large number became symptom-free except for anorexia during the 60 days.

Pulaski, Artz, and Reiss[65] reported that in 153 patients they observed only 6 instances of nausea and vomiting, 10 of diarrhea, and 1 of proctitis. In all cases the symptoms were mild. The symptoms of nausea and vomiting are greatly relieved if a glass of milk is taken with the oxytetracycline.[39]

Spink[69] observed that oxytetracycline rarely caused hypersensitivity reactions in the form of fever and skin eruptions. Our experience has been similar and we have seldom seen the gastrointestinal symptoms become distressing.

Turell and Maynard[73] have found that aside from micrococcic enteritis the anorectocolonic side effects of antibiotics are not of a serious nature. Diarrhea came on about 12 to 72 hours after the antibiotic was started. Itching appeared at the same time or, more commonly, several days after the diarrhea began. About one-half their patients had antecedent symptoms of unstable personalities. Spontaneous recovery occurred in quite a few patients. Local therapy was effective. They believe that acidophilus milk (yogurt) and buttermilk are ineffective in diarrhea or pruritus.

Pseudomembranous enterocolitis. The most serious complication which has been observed in association with the administration of oxytetracycline is pseudomembranous enterocolitis or staphylococcal enteritis. It is not peculiar to oxytetracy-

cline. It has been observed after the administration of several of the antibiotics. It has also been observed in patients receiving no antibiotic. In the past it was frequently fatal. Although the cause is still unknown, present methods of treatment seem to be effective.

The occurrence of pseudomembranous enterocolitis antedates antibiotic therapy and its relationship to the administration of antibiotics is not clearly established. Dixon and Weismann[16] reviewed the subject in 1948 before the days of broad-spectrum antibiotic therapy. Most of the patients in their study had been given chemotherapeutic agents in preparation for operation. But they credited Finney with having first described the entity in 1893 long before the days of chemotherapeutic agents. They had no explanation for the occurrence of the disease in their patients but reviewed the theories which ascribe it to such factors as shock and toxins from systemic infections. They observed that it occurred in association with a great variety of surgical and medical conditions, operations, and in the terminal stages of many constitutional diseases such as cancer and uremia.

Apparently observations of the effect of antibiotics on the flora of the intestinal tract have led to the current keen interest in pseudomembranous enterocolitis and the incrimination of the antibiotics. Only a few of the several recent reports and reviews can be referred to in this discussion.

Herrell, Nichols, and Martin[31] pointed out that pseudomembranous enterocolitis has occurred after the use of sulfaguanidine and streptomycin given orally and after oxytetracycline and streptomycin given parenterally. Dearing and Heilman[13] reported its occurrence after the use of chlortetracycline, chloramphenicol, and oxytetracycline. Fairlie and Kendall[19] observed it after the administration of penicillin and dihydrostreptomycin given parenterally.

Micrococci are not normally found in the intestinal tract. When the normal bacterial flora of the intestine is altered by antibiotics, resistant strains of micrococci may proliferate rapidly and be grown in pure culture from the stool. As stated by Dearing and Heilman,[13] early in the use of chlortetracycline and oxytetracycline, all strains of micrococci encountered were sensitive to chlortetracycline and oxytetracycline. They reported that in a special study of 44 patients with staphylococcal enteritis, 38 of 41 strains of *M. pyogenes* isolated were resistant to streptomycin, chlortetracycline, and oxytetracycline. Herrell, Nichols, and Martin[31] reported that 36 per cent of the strains of *M. pyogenes* studied in 1951 were resistant to chlortetracycline and oxytetracycline and two years later 45 per cent were resistant. As suggested by Dearing and Heilman, pseudomembranous enterocolitis may result from the enterotoxins elaborated by these resistant strains of micrococci.

However, it was found that as many patients died of this disease at the Mayo Clinic in the days before the use of antibiotics. From 1927 to 1936 when no antibiotic agents were available, 42 patients died of pseudomembranous enterocolitis, while from 1943 to 1952, 37 patients died of this disease.[13, 53] The occurrence of pseudomembranous enterocolitis without micrococci in the stool and the growth of pure cultures of micrococci from the stools of persons without symptoms have both been reported.[13, 31, 54] Herrell and Martin suggested that a major stress with the release of large amounts of adrenocortical hormones may in some way increase sus-

ceptibility to invasion by micrococci. Fairlie and Kendall[19] believe the concept that this complication "is due to suppression of normal intestinal flora permitting pathogenic overgrowth of intestinal staphylococci appears to be oversimplified. A direct stimulation of the Staphylococcus by antibiotics must be considered." Prohaska, Govostis, and Taubenhaus[54] had 7 patients with pseudomembranous enterocolitis. Three of the 7 had received no antibiotic. Despite exhaustive cultures they found staphylococci in the stool of only 1 of the 7 patients. They do not believe it results from the overgrowth of staphylococci from treatment with antibiotics.

Whatever the cause of the enterocolitis, it should be appreciated that it may be seen after the administration of oxytetracycline and other antibiotics. It should be suspected in any patient receiving antibiotic treatment who develops diarrhea, exhaustion, anorexia, nausea, vomiting, distention, and fever. None of the symptoms are constant.

Welch[76] suggests that large doses of antibiotics were used in many cases of micrococcic enteritis and a reduction in dosage may reduce the incidence. Combining neomycin with oxytetracycline would appear to decrease the likelihood of the development of resistant strains of *M. pyogenes* when the combination is used for the suppression of intestinal bacteria in preoperative preparation of the bowel or in treatment.[15]

When a patient is suspected of having pseudomembranous enterocolitis, the antibiotic being used should be stopped and smears and cultures made of the stools. If the patient is gravely ill, an antibiotic to which the micrococci are sensitive should be started. Erythromycin has been satisfactory in quickly ameliorating the symptoms.[13, 21, 76] Nyhus[61] used hydrocortisone in addition to erythromycin in a 9 year old boy who developed pseudomembranous enterocolitis after being given chlortetracycline for bronchitis. Although the boy was seriously ill, he recovered. Prohaska, Govostis, and Taubenhaus had 7 patients with pseudomembranous enterocolitis. Four of the 7 died but 3 who were treated with corticotropin survived. They believe treatment with corticotropin is a life saving measure. They do not believe that resistant micrococci are responsible for the disease and emphasize that this is important since corticotropin would be contraindicated in patients with micrococcal enteritis.

Welch[76] expects that strains of micrococci resistant to erythromycin will be encountered. He suggests that chloramphenicol, bacitracin, and carbomycin may be effective in such cases. If micrococci are found in the stool it is advisable to test the sensitivity of the strain to these several agents. Any one might be used while awaiting the results of the test. Because of the strong evidence of cross infection with micrococci in hospitals, a routine check of the sensitivity of micrococci isolated from the stools, noses, and throats of hospitalized patients might be helpful for the treatment of patients in whom micrococcic enteritis developes suddenly.

CHEMISTRY

Oxytetracycline is prepared from a culture of *Streptomyces rimosus*. A product of high purity and constant properties is obtained by several stages of purification involving repeated extraction with n-butanol, formation of acid salts, and chromato-

graphic separation. Oxytetracycline is a pale yellow compound represented by the formula $C_{22}H_{24}N_2O_9$ (mol. wt. 466), and melts at 184.5 to 185.5 C. with decomposition.[60] An extensive investigation by scientists in the Pfizer and Harvard laboratories established the structural formula of oxytetracycline shown in figure 1.[34] Support for this structure was derived from ultraviolet and infrared spectra, alkaline, acid, and reductive degradations, and the preparation of many organic derivatives.

Oxytetracycline is amphoteric and readily forms salts with either acids or bases. The amphoteric form is only slightly soluble in water but the acid and basic salts are readily soluble. Thus oxytetracycline is available for absorption throughout the gastrointestinal tract despite the variation in *p*H. Oxytetracycline is least soluble at its isoelectric point, about *p*H 5.0 as shown in table I. All three forms are soluble in acetone, methanol, ethanol, and other polar organic solvents.[59]

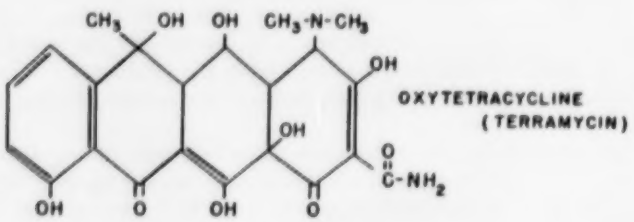

FIGURE 1.

Oxytetracycline is a very stable antibiotic. In the dry state, oxytetracycline and its hydrochloride show no detectable loss in activity on prolonged storage at 25 C. The hydrochloride shows less than 5 per cent inactivation after four months at 56 C., while oxytetracycline shows no loss in potency on heating for four days at 100 C. The yellow sodium salt darkens in light at room temperature and loses potency gradually. Aqueous solutions of the hydrochloride at *p*H 1.0 to 2.5 are stable for at least 30 days at 5 C. and 25 C. Solutions at *p*H 3.0 to 9.0 show no detectable loss in potency on storage at 5 C. for at least one month.[59]

Oxytetracycline has been found to be stable in the presence of serum.[6, 29, 64]

TABLE I

Solubility of Oxytetracycline in Aqueous Solutions at 23 C.

*p*H	Solubility (μg./ml.)	*p*H	Solubility (μg./ml.)
1.2	31,400	6.0	700
2.0	4,600	7.0	1,100
3.0	1,400	8.0	28,000
4.0	850	9.0	38,000
5.0	500		

ROUTES OF ADMINISTRATION AND DOSAGE

Oral. In general, the oral administration of oxytetracycline is the safest, the most convenient, and the most economical method of administration. We are now using smaller doses than originally recommended. A dosage of 250 mg. every six hours will control most infections. The dosage may be doubled in more severe infections. Further increase in the dosage will increase the serum level some but not proportionately. In children under 20 Kg. in weight, dosages of 25 mg. to 50 mg./Kg. daily should be used.

If symptoms of nausea and vomiting are encountered, they can be reduced by administering the drug with milk or food, which do not interfere with its absorption.

If oxytetracycline is being given for preoperative sterilization of the bowel it may be desirable to combine neomycin with it as discussed above under "Antimicrobial Activity." A tablet is available containing 50 mg. of oxytetracycline and 250 mg. of neomycin. For operative preparation of the colon it is recommended that the patient be placed on a low residue diet. After the administration of a cathartic (unless contraindicated), the patient is given 4 tablets every hour for four hours followed by 4 tablets every four hours for 24 to 72 hours before operation. Because of a mild laxative effect of the preparation, the patient usually has several bowel movements. Administration of the drug should not extend beyond 72 hours.

Intravenous. Oxytetracycline is administered parenterally to patients who are unable to take it by mouth or when it is desired to obtain a high serum level quickly. The usual dosage is 0.5 Gm. every 12 hours. The crystalline preparation with its buffer is dissolved in 5 per cent dextrose or normal saline solution for administration. It is recommended that the drug be given in a concentration of not more than 5 mg./ml., in a volume of not less than 100 ml. and at a rate not exceeding 100 ml. in five minutes. In children a dosage of 10 mg. to 25 mg./Kg. of body weight every 12 hours should be used.

Intramuscular. It is often more convenient to give oxytetracycline intramuscularly than intravenously. It should be used in a dosage of 100 mg. every eight hours. In children a dosage of 5 mg. to 10 mg./Kg. of body weight every eight to 12 hours is effective.

Subcutaneous. It is sometimes desirable to give oxytetracycline by subcutaneous clysis, particularly in children. The intravenous preparation may be used for this purpose. It is recommended that it be given in a concentration of 1 mg./ml. of dextrose solution, normal saline, or other electrolyte solution for parenteral use. It should be used in a dosage of 10 mg. to 25 mg./Kg. of body weight every 12 hours.

Topical. A great variety of dermatologic, gynecologic, ophthalmologic, and otologic conditions have been treated successfully by the topical application of oxytetracycline in the form of powder, solution, troche, ointment, paste, salve, or suppository.

BIBLIOGRAPHY

1. Baker, H. J., and Pulaski, E. J.: Effects of terramycin on fecal flora, Ann. New York Acad. Sc. 53: 324, Sept. 15, 1950.
2. Bargen, J. A.: Editorial: Preparation of the patient for intestinal surgery, Surg., Gynec. & Obst. 99:373, September, 1954.
3. Bateman, J. C.; Kloff, C. T., and Samson, R.: Effect of nephrectomy on azotemia associated with parenteral antibiotic administration, *In* Antibiotics Annual, 1953-1954, New York, Medical Encyclopedia, Inc., 1953, pp. 531–534.
4. Bauer, R. E.; Parker, R. T.; Hall, H. E.; Benson, J. F.; Joslin, B. S.; Hightower, J. A.; Snyder, M. J.; Venable, S. J., and Woodward, T. E.: Clinical and experimental observations with terramycin in certain rickettsial and bacterial infections, Ann. New York Acad. Sc. 53:395, Sept. 15, 1950.
5. Benigno, P.; Berti, T., and Cima, L.: Action of erythromycin alone and associated with oxytetracycline and penicillin on *Staphylococcus aureus*, Antib. & Chemo. *4*:1143, November, 1954.
6. Bliss, E. A.; Warth, P. T., and Chandler, C. A.: The susceptibility of Gram-positive cocci, Gram-negative bacilli and clostridia to terramycin, Ann. New York Acad. Sc. 53:277, Sept. 15, 1950.
7. Brannick, T. L.; Martin, W. J.; Gerace, J. E., and Nichols, D. R.: Intramuscular administration of oxytetracycline and studies of its concentration in the serum, Proc. Staff Meet., Mayo Clin. 29:183, April 7, 1954.
8. Broitman, S. A.; Cohen, J. R., and Litsky, W.: A comparison of the effects of terramycin hydrochloride and amphoteric terramycin on the fecal flora of humans, Am. J. M. Sc. *226*:419, October, 1953.
9. Bumbalo, T. S., and Gustina, F. J.: The treatment of pinworm infection in children, Postgrad. Med. *14*:83, July, 1953.
10. Bryson, V., and Demerec, M.: Patterns of resistance to antimicrobial agents, Ann. New York Acad. Sc. 53:283, Sept. 15, 1950.
11. Danopoulos, E.; Angelopoulos, B.; Zioudrou, C., and Amira, P.: Experimental study on the absorption of oxytetracycline by the stomach and the small intestine and its excretion in the bile, Antib. & Chemo. *4*:451, April, 1954.
12. Davis, H. L.: A study of the mechanisms and evaluation of antiseptic actions, J. Soc. Cosmetic Chemists 2:295, 1951.
13. Dearing, W. H., and Heilman, F. R.: Micrococcic (staphylococcic) enteritis as a complication of antibiotic therapy: Its response to erythromycin, Proc. Staff Meet., Mayo Clin. *28*:121, March 11, 1953.
14. Dearing, W. H., and Needham, G. M.: The effect of terramycin on the intestinal bacterial flora of patients being prepared for intestinal surgery, Proc. Staff Meet., Mayo Clin. *26*:49, Jan. 31, 1951.
15. Dearing, W. H., and Needham, G. M.: Effect of oral administration of neomycin and oxytetracycline (terramycin) on the intestinal bacterial flora of man, Proc. Staff Meet., Mayo Clin. *28*:507, Sept. 9, 1953.
16. Dixon, C. F., and Weismann, R. E.: Acute pseudomembranous enteritis or enterocolitis: A complication following intestinal surgery, S. Clin. North America *28*:999, August, 1948.
17. Edmiston, J. M.; Davies, O. G.; Ledwich, T. W.; Marchi, F.; Shafer, M., and McCorkle, H. J.: Experimental evaluation of intestinal antiseptics when used for protection from fecal contamination during colon resection, Surg., Gynec. & Obst. *92*:641, June, 1951.
18. Eisenberg, G. M.; Flippin, H. F., and O'Loughlin, J. M.: Bacterial susceptibility to antibiotics. V. Relative susceptibility of staphylococci and enterococci to erythromycin, carbomycin and a combination of chlortetracycline, oxytetracycline and chloramphenicol, Antib. & Chemo. 3:1026, October, 1953.
19. Fairlie, C. W., and Kendall, R. E.: Fatal Staphylococcus enteritis following penicillin and streptomycin therapy, J.A.M.A. *153*:90, Sept. 12, 1953.
20. Farley, W. J., and Konieczny, L.: Terramycin by subcutaneous clysis, J. Pediat. *42*:177, February, 1953.
21. Finland, M.; Gocke, T. M.; Jackson, G. G.; Womack, C. R., and Kass, E. H.: Clinical studies on terramycin, Ann. New York Acad. Sc. 53:290, Sept. 15, 1950.
22. Finlay, A. C.; Hobby, G. L.; P'an, S. Y.; Regna, P. P.; Routien, J. B.; Seeley, D. B.; Shull, G. M.; Sobin, B. A.; Solomons, I. A.; Vinson, J. W., and Kane, J. H.: Terramycin, a new antibiotic, Science *111*:85, Jan. 27, 1950.

23. Gocke, T. M.; Jackson, G. G.; Wilcox, C., and Finland, M.: In vitro studies on terramycin, Ann. New York Acad. Sc. 51:297, Sept. 15, 1950.
24. Greene, H. J.: Terramycin in the treatment of *Trichomonas vaginalis* vaginitis; a report of 21 cases, Antib. & Chemo. 2:119, March, 1952.
25. Gronroos, J. A., and Kalliomaki, L.: Failure of cation exchange resin to impair intestinal absorption of terramycin, Scandinav. J. Clin. & Lab. Invest. 5:378, 1953.
26. Hammond, C. W., and Miller, C. P.: The effects of terramycin on postirradiation infection in mice, Ann. New York Acad. Sc. 51:303, Sept. 15, 1950.
27. Helander, S., and Bottiger, L. E.: On the distribution of terramycin in different tissues, Acta. med. Scandinav. *147*:71, 1953.
28. Hendricks, F. D.; Greaves, A. B.; Olansky, S.; Taggart, S. R.; Lewis, C. N.; Landman, G. S.; MacDonald, G. R., and Welch, H.: Terramycin in the treatment of venereal disease, J.A.M.A. *141*: 4, May 6, 1950.
29. Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Some bacteriologic, pharmacologic, and clinical observations on terramycin, Ann. New York Acad. Sc. 51:448, Sept. 15, 1950.
30. Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. G.: Terramycin: Some pharmacologic and clinical observations, Proc. Staff Meet., Mayo Clin. 25:183, April 12, 1950.
31. Herrell, W. E.; Nichols, D. R., and Martin, W. J.: Erythromycin for infections due to Micrococcus pyogenes, J.A.M.A. *152*:1601, Aug. 23, 1953.
32. Hobby, G. L.: Symposium on the mode of action of antibiotics: Part II. The mode of action of terramycin and aureomycin, Bact. Rev. *17*:29, March, 1953.
33. Hobby, G. L.; Lenert, T. F.; Pikula, D.; Kiseluk, M., and Huddleson, E.: The antimicrobial action of terramycin, Ann. New York Acad. Sc. 51:266, Sept. 15, 1950.
34. Hochstein, F. A.; Stephens, C. R.; Conover, L. H.; Regna, P. P.; Pasternack, R.; Bruninos, K. J., and Woodward, R. B.: Terramycin. VII. The structure of terramycin, J. Am. Chem. Soc. *74*:3708, July 20, 1952.
35. Hoffman, M. S.; Wellman, W. E., and Herrell, W. E.: Failure of absorption of aureomycin and terramycin administered as a retention enema, Proc. Staff Meet., Mayo Clin. 25:463, Aug. 2, 1950.
36. Johnston, T. G., and Cazort, A. G.: Severe serum sickness reaction with cyanosis following terramycin, Antib. & Chemo. 3:481, May, 1953.
37. Kagan, B. M.; Mendelsohn, R. S.; Miller, R. A., and Elegant, L. D.: Subcutaneous administration of oxytetracycline, Antib. & Chemo. *4*:308, March, 1954.
38. Kass, E. H.; Barnes, M. W., and Finland, M.: Terramycin in influenza viral infections, Ann. New York Acad. Sc. 51:412, Sept. 15, 1950.
39. Kendig, E. L., Jr., and Arnold, G. G.: Oxytetracycline in the treatment of pinworm infestation, Antib. & Chemo. *4*:1111, October, 1954.
40. Kirby, W. M. M., and Ahern, J. J.: Changing pattern of resistance of staphylococci to antibiotics, Antib. & Chemo. 3:831, August, 1953.
41. Kneeland, Y., Jr., and Melcher, G. W.: Terramycin in the treatment of primary atypical pneumonia, Ann. New York Acad. Sc. 51:437, Sept. 15, 1950.
42. Knight, V.: Chemotherapy of brucellosis, Ann. New York Acad. Sc. 51:332, Sept. 15, 1950.
43. Lane, S. L.; Kutscher, A. H., and Chaves, R.: Oxytetracycline in the treatment of orocervical facial actinomycosis, J.A.M.A. *151*:986, March 21, 1953.
44. Linsell, W. D., and Fletcher, A. P.: Laboratory and clinical experience with terramycin hydrochloride, Brit. M. J. 2:1190, Nov. 25, 1950.
45. McKittrick, L. S.: Editorial: The surgeon's bib, Surg., Gynec. & Obst. 99:374, September, 1954.
46. Michel, J. C.; Sayer, R. J., and Kirby, W. M. M.: Effect of food and antacids on blood levels of aureomycin and terramycin, J. Lab. & Clin. Med. *36*:632, October, 1950.
47. Miller, F. L.; Sands, J. H.; Walker, R.; Dye, W. E., and Temple, C. W.: Combined daily terramycin and intermittent streptomycin in the treatment of pulmonary tuberculosis, Am. Rev. Tuber. *66*:534, November, 1952.
48. Miura, Y.; Nakamura, Y.; Yoshizawa, Y., and Matsudaira, H.: Comparative studies on the phosphorus metabolism of staphylococci in the presence of chlortetracycline and oxytetracycline, Antib. & Chemo. 3:822, August, 1953.

49. Monthorency, F. A., Caffery, E. L., and Musselman, M. M.: Observations on the use of oxytetracycline intramuscularly, Antib. & Chemo. *4*:313, March, 1954.
50. Nelson, A. A., and Radomski, J. L.: Comparative pathological study in dogs of feeding of six broad-spectrum antibiotics, Antib. & Chemo. *4*:1174, November, 1954.
51. Nyhus, R. E., and Burke, E. C.: Pseudomembranous enterocolitis: Medical treatment, with recovery, Proc. Staff Meet., Mayo Clin. *29*:513, Sept. 1, 1954.
52. P'an, S. Y., Scaduto, L., and Cullen, M.: Pharmacology of terramycin in experimental animals, Ann. New York Acad. Sc. *51*:238, Sept. 15, 1950.
53. Pettet, J. D., Baggenstoss, A. H., Judd, E. S., Jr., and Dearing, W. H.: Generalized postoperative pseudomembranous enterocolitis, Proc. Staff Meet., Mayo Clin. *29*:342, June 16, 1954.
54. Prohaska, J. V., Govoni, M. C., and Taubenhaus, M.: Postoperative pseudomembranous enterocolitis: Treatment with corticotropin (ACTH), J.A.M.A. *154*:320, Jan. 23, 1954.
55. Pulaski, E. J., Artz, C. P., and Reis, E.: Terramycin and aureomycin in surgical infections, report of two hundred cases, J.A.M.A. *149*:35, May 3, 1952.
56. Quilligan, J. J., Jr., Francis, T., Jr., Rowe, R. J., Traood, D. G., Adcock, J. D., and Kurtz, H.: The action of terramycin on the growth of strains of influenza, herpes simplex, and rabies viruses in chick embryos and mice, Ann. New York Acad. Sc. *51*:407, Sept. 15, 1950.
57. Rantz, L. A., and Randall, E.: Antibiotic synergism and *Staphylococcus aureus*, Antib. & Chemo. *2*:645, December, 1952.
58. Regna, P. P.: Chemical structure of terramycin in relation to mode of action, Tr. New York Acad. Sc. *15*:12, November, 1952.
59. Regna, P. P., and Solomons, I. A.: The chemical and physical properties of terramycin, Ann. New York Acad. Sc. *51*:229, Sept. 15, 1950.
60. Regna, P. P., Solomons, I. A., Murai, K., Timbeck, A. E., Brunings, K. J., and Lazier, W. A.: The isolation and general properties of terramycin and terramycin salts, J. Am. Chem. Soc. *73*:4211, September, 1951.
61. Rhoads, P. S., Billings, C. E., and Adair, D. M.: Study of the *in vitro* activity of antibiotics and sulfonamides, singly and in combinations against microorganisms of the urinary tract, Antib. & Chemo. *3*:721, July, 1953.
62. Rose, H. M.: The experimental and clinical evaluation of terramycin against Rickettsia akari (rickettsialpox), Ann. New York Acad. Sc. *51*:385, Sept. 15, 1950.
63. Schatten, W. E., and Abbott, W. E.: Intraperitoneal administration of terramycin in the treatment of experimental peritonitis, Surg., Gynec. & Obst. *97*:445, October, 1953.
64. Schoenbach, E. B., Bryer, M. S., and Lono, P. H.: The pharmacology of terramycin in animals and man with reference to its clinical trial, Ann. New York Acad. Sc. *51*:245, Sept. 15, 1950.
65. Seidwitz, J., Bateman, J. C., and Klopp, C. T.: Oxytetracycline toxicity studies in dogs, Antib. & Chemo. *3*:1015, October, 1953.
66. Smadel, J. E., Jackson, E. B., and Ley, H. L., Jr.: Terramycin as a rickettsiostatic agent and its usefulness in patients with scrub typhus, Ann. New York Acad. Sc. *51*:375, Sept. 15, 1950.
67. Snyder, J. C., Fadan, R., Wells, E. B., Wick, H. C., and Miller, J. D.: Experimental studies on the antirickettsial properties of terramycin, Ann. New York Acad. Sc. *51*:362, Sept. 15, 1950.
68. Spaulding, E. H., Tyson, R. R., and Casey, J. A.: The fecal flora during prolonged administration of terramycin, Bact. Proc. *52*:113, 1952.
69. Spink, W. W.: Clinical problems relating to the management of infections with antibiotics, J.A.M.A. *152*:585, June 13, 1953.
70. Steenken, W., Jr., and Wolinsky, E.: The tuberculostatic action of terramycin *in vitro* and in the experimental animal, Ann. New York Acad. Sc. *51*:309, Sept. 15, 1950.
71. Taylor, W. I., and Novak, M.: Antibiotic prophylaxis of experimental clostridial infections. I. Antibiotic prophylaxis of tetanus, Antib. & Chemo. *2*:517, October, 1952.
72. Taylor, W. I., and Novak, M.: Antibiotic prophylaxis of experimental clostridial infections. III. Antibiotic prophylaxis of gas gangrene, Antib. & Chemo. *2*:639, December, 1952.
73. Turell, R., and Maynard, A. de L.: Anorectocolonic side effects of antibiotic therapy, J.A.M.A. *156*:217, Sept. 18, 1954.

74. Weinberg, E. D.: The influence of inorganic salts on the activity *in vitro* of oxytetracycline, Antib & Chemo. *4*:35, January, 1954.
75. Welch, H.: Absorption, excretion and distribution of terramycin, Ann. New York Acad. of Sc. 51: 253, Sept. 15, 1950.
76. Welch, H.: Editorial: The antibiotic-resistant staphylococci, Antib. & Chemo. 3:561, June, 1953.
77. Welch, H.; Hendricks, F. D.; Price, C. W., and Randall, W. A.: Comparative studies on terramycin and aureomycin: Antibacterial spectrum, serum concentrations and urinary excretion, J. Am. Pharm. A. (Scient. Ed.) 39:185, April, 1950.
78. Welch, H.; Lewis, C. N., and Kerlan, I.: Blood dyscrasias; a nationwide survey, Antib. & Chemo. *4*:607, June, 1954.

biographical note

Doctor Merle McNeil Musselman was born in Topeka, Kansas, in 1915. He studied at the University of Omaha and the University of Nebraska, and in 1939 received his doctorate in medicine from the College of Medicine of the latter university. From 1946 to 1949 he worked for his master of science degree at the University of Michigan.

Doctor Musselman interned at the Long Island College Hospital, Brooklyn, N. Y., and he was a resident physician at the University Hospital, Ann Arbor, Mich. His appointments include positions as a professor of surgery at the University of Nebraska College of Medicine and as a consultant in surgery at the Veterans' Administration Hospital, Omaha, Nebr.

Merle M. Musselman, M.D.

From July 1, 1941 to August 6, 1946, Dr. Musselman served in the Army Medical Corps. At the time of his discharge, with the rank of captain, he had merited the Bronze Star. Since that time he has been a member of the active reserve. His present rank is that of major.

Among Dr. Musselman's professional affiliations are membership in the American Association for the Advancement of Science, the American Association of the Surgery of Trauma, the American Board of Surgery, the American College of Surgeons, the American Federation for Clinical Research, the American Medical Association, the Central Surgical Association, the New York Academy of Sciences, and the Omaha Midwest Clinical Society.

In addition to his other activities, Dr. Musselman is the co-author of several books on thrombotic diseases, including *Antithrombic Activity after Operation in Thrombotic Diseases, in Liver Diseases and Other Diseases* and *Pancreatic Venous Thrombosis as an Etiologic Factor in Acute Necrotizing Hemorrhagic Pancreatitis*.

He has also written articles describing various phases of his work for such publications as Antibiotics and Chemotherapy, the Journal of the American Medical Association, Surgery, Gynecology and Obstetrics; Surgery, the Journal of Nutrition, the Journal of Urology, Annals of Surgery, the Bulletin of the American College of Surgeons, the Archives of Surgery, and many other scientific publications.

Oxytetracycline in General Medicine

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INTRODUCTION

Oxytetracycline* has clearly established itself as an exceedingly effective antibiotic in the treatment of a number of so-called medical infections. That oxytetracycline diffuses readily into most body tissues was evident from the early report on its pharmacologic behavior published by Herrell et al.[1] Following the oral administration of single therapeutically effective doses, adequate levels of the antibiotic in the serum were maintained for six to eight hours. Following the administration of single doses by the intravenous route, adequate concentrations of the antibiotic in the serum were maintained for approximately twelve hours. Oxytetracycline was found to diffuse readily into the pleural fluid and also through the placenta. In the noninflamed central nervous system, it does not diffuse readily into the cerebrospinal fluid. Oxytetracycline is concentrated in the liver and excreted readily in a biologically active form in the bile. It is also readily excreted by the kidneys and appears in high concentrations in the urine. When given by the oral route, large amounts of the antibiotic are unabsorbed and excreted in the feces.

INFECTIONS OF THE RESPIRATORY SYSTEM

Pneumococcal Pneumonia. Practically all strains of *Diplococcus pneumoniae* are reasonably sensitive to the inhibitory action of oxytetracycline. The in vitro studies reported by Dowling and his colleagues[5] indicated that there is no significant difference in the concentrations of oxytetracycline and of chlortetracycline† required to inhibit the growth of pneumococci. The concentrations of oxytetracycline required were in such a range that good clinical results could be anticipated. Furthermore, oxytetracycline was found to be considerably more active than chloramphenicol against the strains of *D. pneumoniae* studied. It was clearly evident from the report of Hubbard and Tillett[6] that oxytetracycline was very effective clinically in the treatment of uncomplicated pneumococcal lobar pneumonia. Likewise, Timpanelli and his colleagues[7] concluded from a study of 66 cases of pneumococcal pneumonia that the results of treatment could be classified as excellent by all commonly accepted criteria. They further reported excellent therapeutic results in 34 cases with pneumonias of various types and extents.

The recommended oral dose of oxytetracycline is 500 to 750 mg. every six hours. In seriously ill patients who are unable to swallow, the intravenous or intramuscular preparations of oxytetracycline are recommended.

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*The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

†The trade name of Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline is Aureomycin.

Staphylococcal Pneumonia. When oxytetracycline was first introduced for clinical use, practically all strains of *Micrococcus pyogenes* were sensitive to its action. Excellent results were therefore obtained using it in the treatment of the occasional infection in the respiratory tree owing to this organism. The ability of *M. pyogenes* to develop resistance to antibiotics is well known to everyone. Therefore, it is not surprising that at the present time probably no more than half of the strains of *M. pyogenes* isolated from secretions from the tracheobronchial tree are sensitive to oxytetracycline. When the organism isolated is found to be sensitive to the antibiotic, oxytetracycline can be used satisfactorily in the treatment of staphylococcal pneumonia. On the other hand, if the organism is found to be resistant to oxytetracycline, the clinical investigator must use one of the newer antibiotics or a combination of antibiotics that is inhibitory.

Primary Atypical Pneumonia. Most investigators readily agree that the evaluation of antibiotic therapy in so-called primary atypical ("viral") pneumonia is difficult. However, from the report of Kneeland and Melcher[8] it would appear that oxytetracycline was effective in the treatment of a limited number of cases of primary atypical pneumonia in which penicillin in adequate doses had been found to be ineffective. Final evaluation of the effectiveness of oxytetracycline in the treatment of this infection must await further investigations. Recent evaluations of oxytetracycline in atypical pneumonia, such as those of Blattner,[26] Finland,[27] Graves and Ball,[28] James,[29] Kneeland and Melcher,[8] and Meiklejohn and co-workers[30] make it appear that it has real value.

Primary Pneumonia Owing to Hemophilus influenzae. Primary pneumonia caused by *Hemophilus influenzae* is rare. Crowell and Loube[9] report that it occurs in less than 0.1 per cent of all pneumonias observed in their experience. They further report four cases of this type of pneumonia and concluded that oxytetracycline was as effective as either streptomycin or chloramphenicol. In view of the well-known toxic reactions that may be associated with or follow the use of the latter two antibiotics, it seems reasonable at the moment to recommend oxytetracycline in the treatment of pneumonia caused by *H. influenzae.*

Pertussis. Jackson and his colleagues[10] reported studies on the comparison of oxytetracycline with six other antibiotics in the treatment of experimental infections with *Hemophilus pertussis* in embryonated hens' eggs. They concluded that oxytetracycline was somewhat superior to the other six antibiotics. From a preliminary clinical trial in a small number of patients they also concluded that oxytetracycline exerted a favorable bacteriologic and clinical effect on whooping cough. Subsequent studies by Bogdan[11] suggested that, if given early in the preparoxysmal stage of whooping cough, oxytetracycline can modify and arrest the course of the disease. According to him the onset of paroxysms may be averted and the duration of the illness and infectivity shortened. He further pointed out that immunity may not follow arrest of the illness in the preparoxysmal stage and for that reason suggested that for ultimate protection immunization still may be advisable. At the time of this writing not enough clinical material has been reported to warrant any final statement concerning the value of oxytetracycline in the treatment of pertussis.

However, continuing favorable reports on the treatment of pertussis by oxytetracycline are accumulating.[31–34] Further trials would seem indicated.

INFECTIONS OF THE BLOOD STREAM AND HEART

Bacteremia. The success of treatment of uncomplicated bacteremia with oxytetracycline depends upon early diagnosis and adequate treatment. As a rule pneumococcal, streptococcal, and staphylococcal bacteremia respond in a satisfactory manner to treatment with oxytetracycline provided the organism isolated is sensitive to the antibiotic in a range that is attainable in the blood stream.

Best results in the treatment of bacteremia owing to organisms of the coliform group will be obtained with a combination of oxytetracycline and dihydrostreptomycin. Likewise, a combination of these two antibiotics is the method of choice in the treatment of bacteremia owing to *Proteus vulgaris* or *Aerobacter aerogenes*.

In the past bacteremia due to *Bacteroides fundulíformis* has been highly fatal. A number of patients with bacteremia caused by this organism have been satisfactorily treated using full therapeutic doses of oxytetracycline by either the oral or the intravenous route. It is essential in the successful treatment of this infection that therapy with oxytetracycline be intensive and prolonged (at least three to four weeks).

For adult patients the recommended dose of oxytetracycline in the treatment of bacteremia is at least 3 Gm. by the oral route each 24 hours. This is administered in amounts of 750 mg. every six hours. For administration by the intravenous route the recommended dose is 1 Gm. per day (500 mg. every 12 hours). Details regarding dosage and methods of administration will be discussed later.

Subacute Bacterial Endocarditis. Oxytetracycline is primarily a bacteriostatic agent. Although most strains of *Streptococcus mitis* are sensitive to its action, it has not proved of great value in the treatment of subacute bacterial endocarditis and therefore is not recommended in the treatment of this disease.

BRUCELLOSIS

Because of the development of combinative therapy the effectiveness of oxytetracycline in brucellosis has exceeded its early promise. It was evident from some studies reported by Heilman[12, 13] that none of the available broad-spectrum antibiotics (chloramphenicol, chlortetracycline, or oxytetracycline) used alone was particularly effective in controlling experimentally produced brucella infections in animals. Clinical investigations were consistent with these observations. When any one of these antibiotics was used alone in the treatment of brucellosis, the relapse rate was high.

It was further evident from the studies of Heilman that a combination of either chlortetracycline or oxytetracycline with dihydrostreptomycin was the most effective form of treatment of experimentally produced infections. Clinical investigation of the use of combined antibiotic therapy of brucellosis reported by Herrell and Barber[14–16] confirmed the validity of these observations. In the treatment of 60 cases of culturally proved brucellosis, we experienced a recovery rate of 95 per cent with a

clinical-bacteriologic relapse rate of only 5 per cent. These cases were followed over periods of from three months to more than two years. Therefore, it seems clearly established that oxytetracycline is sufficiently effective in the treatment of culturally proved brucellosis only when it is combined with dihydrostreptomycin. The method of treatment consists of the simultaneous administration of oxytetracycline, 3 Gm. by the oral route every 24 hours (in divided doses of 750 mg. every six hours), and dihydrostreptomycin, 1 Gm. by the intramuscular route every 12 hours. In the treatment of bacteremic brucellosis the administration of the antibiotics should be continued for 12 to 14 days. In the treatment of focal brucellosis, therapy should be continued for 28 days, using the same daily dose of oxytetracycline but reducing the dose of dihydrostreptomycin to 0.5 Gm. twice daily by the intramuscular route. To date this combination of antibiotics remains the most effective method of treating this disease.

VIRAL AND RICKETTSIAL INFECTIONS

Viral Infections. As was indicated earlier, there is little or no experimental or clinical evidence to confirm that oxytetracycline is of value in the treatment of the commonly encountered viral infections. Certainly it has no place in the primary treatment of the common cold, influenza, poliomyelitis, encephalitis, measles, chickenpox, smallpox, rabies, or herpes (either simple or zoster). If oxytetracycline has any role whatsoever in the treatment of these viral infections, it is in the possible control of secondary infection.

There is some experimental and clinical evidence to suggest that oxytetracycline may be effective in the treatment of certain viral diseases. Pollard and his colleagues[17] reported the successful use of the antibiotic in the treatment of psittacosis. Henley[18] reported that oxytetracycline was significantly more effective in the treatment of early lymphogranuloma venereum than was the standard method of treatment using sulfonamides and antimony. That oxytetracycline should be effective in the treatment of the so-called psittacosis-lymphogranuloma infections is interesting in the light of the recent tendency to consider these two viruses as probably belonging to the classification of rickettsiales.

Rickettsial Infections. It was evident from the study reported by Rose[19] that oxytetracycline was highly effective in the treatment of experimental and clinical rickettsialpox. Smadel and his colleagues[20] reported that oxytetracycline was more active than either chlortetracycline or chloramphenicol in the treatment of experimental infections with the agent of Q fever. From the same report it was evident that oxytetracycline also possessed considerable activity against the rickettsia of scrub typhus. Bauer and his colleagues[21] reported oxytetracycline to be effective also in the treatment of Rocky Mountain spotted fever and murine typhus.

From these and other studies there can be little doubt concerning the rickettsiostatic activity of oxytetracycline. The recommended dose of this antibiotic in the treatment of rickettsial infections is 2 to 3 Gm. daily given by the oral route in four divided doses. In patients who for any reason cannot take the antibiotic by the oral route, it is recommended that it be given by the intravenous route in amounts of 0.5 Gm. every 12 hours.

BASIC CONSIDERATIONS OF ETIOLOGY

From in vitro studies it is evident that oxytetracycline has a wide range of antibacterial activity (broad spectrum). Among the organisms that early were found to be sufficiently sensitive to warrant clinical trials were practically all strains of *D. pneumoniae* and *Streptococcus pyogenes*, and many other bacteria. At the time oxytetracycline was introduced most strains of *M. pyogenes* were found to be readily inhibited by it. However, as experience has accumulated, it has become evident that many strains of this organism may become resistant to oxytetracycline after sufficient exposure to it. *Neisseria meningitidis* and *Neisseria gonorrhoeae* are sensitive to oxytetracycline as are *H. influenzae* and, to some degree, *H. pertussis*. *Brucella abortus*, *suis*, and *melitensis* are inhibited by oxytetracycline in vitro; however, studies in animals indicate that its effect in vivo is only suppressive. The therapeutic effectiveness is considerably augmented by combining it with dihydrostreptomycin. *Pasteurella pestis* and *Pasteurella tularensis* are also sensitive to oxytetracycline. The clostridia are quite sensitive to this antibiotic and are readily eliminated from the stools of patients who are receiving it. Oxytetracycline is highly active against *B. fundulifformis*. It is inhibitory for many of the gram-negative rods. Most strains of *Escherichia coli* are reasonably sensitive to oxytetracycline. This antibiotic also has considerable activity against *A. aerogenes*, *Klebsiella pneumoniae*, and the *Salmonella*. Only a few strains of *Pseudomonas aeruginosa* are inhibited by oxytetracycline. Its activity against *Mycobacterium tuberculosis* is not sufficient to warrant its use as the principal agent for the treatment of tuberculosis, but it is often a useful adjuvant. It was evident from the report of Snyder and his colleagues[2] that oxytetracycline possesses antirickettsial activity. They found the antibiotic to be active against the *Rickettsiae* of epidemic and murine typhus, Rocky Mountain spotted fever, rickettsialpox, and scrub typhus. It was found to be somewhat more active in experimentally infected chick embryos than chlortetracycline or chloramphenicol. Subsequent studies have confirmed the fact that it is also highly effective in the treatment of clinical infections caused by *Rickettsiae*. It appeared from studies by Quilligan and his colleagues[3] that oxytetracycline had a mildly suppressive effect on the multiplication of the influenza virus. Its activity, however, was not of sufficient degree to suggest that it would be of any value in the treatment of clinical influenza. There is little or no experimental or clinical evidence to confirm that oxytetracycline is of value in the treatment of any of the commonly encountered respiratory viral diseases except atypical ("viral") pneumonia. That oxytetracycline displayed inhibitory action against *Endamoeba histolytica* was evident from the early report of Most and Van Assendelft.[4] Subsequent studies have established its value in the treatment of intestinal amebiasis. Oxytetracycline has appeared to have little or no activity against some of the other intestinal parasites and helminths.

DOSAGE AND METHODS OF ADMINISTRATION

For reasons that were apparent in some studies on absorption and diffusion of oxytetracycline, it has become a policy to administer the antibiotic every six hours by the oral route. In my experience, 500 to 750 mg. is an adequate and effective thera-

peutic dose given orally to adults. This represents approximately 2 to 3 Gm. of the antibiotic every 24 hours and approximately 30 to 45 mg./Kg. of body weight. Increasing the oral dose beyond this amount does not materially increase the concentration of oxytetracycline in the serum but appears to increase the incidence of gastrointestinal irritation. To date the most effective method of controlling nausea or vomiting in my experience is to administer oxytetracycline with cold, pasteurized milk. The patient simply swallows one capsule at a time with cold milk instead of water. Giving the antibiotic near the time of intake of food also is helpful. Milk does not interfere with the absorption of oxytetracycline. If for any reason the patient cannot tolerate milk or if one is desirous of avoiding milk because the patient is on a low residue diet, another method of controlling nausea and vomiting is to administer oxytetracycline with sodium bicarbonate, one 5 mg. tablet of the latter for each 250 mg. capsule of the former.

When for any reason the patient is unable to take the antibiotic by the oral route, the intravenous preparation of oxytetracycline is effective. The average daily dose for adults, which I use, is 1 Gm. per day, administered in amounts of 0.5 Gm. every 12 hours. The intravenous preparation is dissolved in the buffer (approximately 15 ml. of buffer) and added to 200 ml. of physiologic saline or glucose solution. The material is allowed to infuse at a fairly rapid rate. The entire amount is given into the vein of the upper extremity twice per day. Caution must be exercised to prevent the injection of concentrated oxytetracycline solutions into the tissues. Considerable irritation in the tissue may occur if the concentrated material is injected outside of the vein. On occasion the recommended amount of the intravenous preparation, which has been dissolved in the buffer, may be added to a liter of physiologic saline and given by means of intravenous drip.

A preparation of oxytetracycline that is satisfactory for intramuscular administration is now available. The recommended dose is 100 mg. every six hours given deep into the muscles of the buttocks. Montmorency and his colleagues[22] have had considerable experience with this preparation. They report satisfactory levels of oxytetracycline in the serum following intramuscular injection (1880 injections in 313 individuals). Brannick and his colleagues[23] also reported on the use of an intramuscular preparation of oxytetracycline in 35 patients with only a few local reactions.

Farley and Konieczny[24] have reported satisfactory clinical use of a purified solution of oxytetracycline given by means of subcutaneous clysis in infants and children. They recommend that a concentration of 1 mg./ml. be routinely employed with a dosage of 10 mg./Kg. of body weight every 12 hours in average infections. In more serious infections they have administered as much as 20 to 25 mg./Kg. of body weight every 8 to 12 hours. Likewise Kagan and his associates[25] have also found the intravenous preparation of oxytetracycline useful when given subcutaneously in the treatment of infections in infants less than 1 year of age.

On occasion it may be desirable to deliver concentrations of oxytetracycline into the intestinal tract in a patient who is unable to swallow. In such an instance oxytetracycline may be given via a nasal tube, which is in place for the purpose of continuous suction. The usual oral dose of oxytetracycline can be removed from the capsule and suspended in milk or feeding formula and introduced into the gastro-

intestinal tract through the tube. If the nasal tube is then clamped for a period of two hours, absorption will occur.

SUMMARY

Oxytetracycline is highly effective in the treatment of pneumococcal pneumonia. It is also effective in the treatment of primary pneumonia owing to *H. influenzae*. It may be of some value in the treatment of primary atypical pneumonia. It may also exert a suppressive effect in the treatment of pertussis.

Oxytetracycline is highly effective in the treatment of pneumococcal and streptococcal bacteremia. It is also effective in the treatment of staphylococcal bacteremia in those instances in which the organism is sensitive to its action. Best results in the treatment of bacteremia owing to organisms of the coliform group will be obtained using a combination of oxytetracycline and dihydrostreptomycin. Bacteremia due to *B. funduliformis* may be successfully treated using oxytetracycline alone. Oxytetracycline is not recommended in the treatment of subacute bacterial endocarditis owing to *S. mitis*.

Oxytetracycline is of value in the treatment of bacteremic and localizing brucellosis only when it is combined with dihydrostreptomycin.

Oxytetracycline is of little or no value in the treatment of many commonly encountered viral diseases. It is highly effective in the treatment of rickettsial infections.

BIBLIOGRAPHY

1. Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. G.: Terramycin: some pharmacologic and clinical observations, Proc. Staff Meet., Mayo Clin. 25:183–196, April 12, 1950.
2. Snyder, J. C.; Fagan, R.; Wells, E. B.; Wick, H. C., and Miller, J. C.: Experimental studies on the antirickettsial properties of terramycin, Ann. New York Acad. Sc. 53:362–374, Sept. 15, 1950.
3. Quilligan, J. J., Jr.; Francis, T., Jr.; Rowe, R. J.; Tragon, D. G.; Adcock, J. D., and Kurtz, H.: The action of terramycin on the growth of strains of influenza, herpes simplex, and rabies viruses in chick embryos and mice, Ann. New York Acad. Sc. 53:407–411, Sept. 15, 1950.
4. Most, H., and Van Amerongen, F.: Laboratory and clinical observations on the effect of terramycin in the treatment of amebiasis, Ann. New York Acad. Sc. 53:427–428, Sept. 15, 1950.
5. Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., and Spies, H. W.: Terramycin in the treatment of pneumococcic and other bacterial infections, Ann. New York Acad. Sc. 53:433–436, Sept. 15, 1950.
6. Hubbard, W. N., Jr., and Tillett, W. S.: Terramycin in the treatment of pneumococcal pneumonia, Ann. New York Acad. Sc. 53:429–432, Sept. 15, 1950.
7. Timpanelli, A.; Huebner, R. D., and McDermott, W.: Terramycin in the treatment of pneumococcal and mixed bacterial pneumonias, Ann. New York Acad. Sc. 53:440–447, Sept. 15, 1950.
8. Kneeland, Y., Jr., and Melcher, G. W.: Terramycin in the treatment of primary atypical pneumonia, Ann. New York Acad. Sc. 53:437–439, Sept. 15, 1950.
9. Crowell, J., and Loube, S. D.: Primary Hemophilus influenzae pneumonia; report of four cases, A. M. A. Arch. Int. Med. 93:921–927, June, 1954.
10. Jackson, G. G.; Chang, S.-M.; Barnes, M. W., and Finland, M.: Terramycin in pertussis: clinical and laboratory studies, Ann. New York Acad. Sc. 53:422–426, Sept. 15, 1950.
11. Bodan, A.: Terramycin in pertussis, Brit. M. J. 2:1186–1187, Nov. 29, 1952.
12. Heilman, F. R.: The effect of combined treatment with aureomycin and dihydrostreptomycin on Brucella infections in mice, Proc. Staff Meet., Mayo Clin. 24:133–137, Mar. 16, 1949.
13. Heilman, F. R.: Personal communication to the author.

14. Herrell, W. E., and Barber, T. E.: The combined use of aureomycin and dihydrostreptomycin in the treatment of brucellosis, Proc. Staff Meet., Mayo Clin. *24*:138–145, Mar. 16, 1949.
15. Herrell, W. E., and Barber, T. E.: A new method for treatment of brucellosis, J. A. M. A. *144*:519–524, Oct. 14, 1950.
16. Herrell, W. E., and Barber, T. E.: Treatment of brucellosis with aureomycin or terramycin combined with dihydrostreptomycin, Postgrad. Med. *11*:476–486, June, 1952.
17. Pollard, M.; Bussell, R. H.; Benedict, A. A., and Wilson, R.: The response of three human infections of psittacosis to antibiotic therapy, Antib. & Chemo. *4*:138–140, Feb. 1, 1954.
18. Henley, K. S.: Terramycin in early lymphogranuloma venereum, Brit. J. Ven. Dis. *29*:36–38, Mar. 1, 1953.
19. Rose, H. M.: The experimental and clinical evaluation of terramycin against *Rickettsia akari* (rickettsialpox), Ann. New York Acad. Sc. *53*:385–394, Sept. 15, 1950.
20. Smadel, J. E.; Jackson, E. B., and Ley, H. L., Jr.: Terramycin as a rickettsiostatic agent and its usefulness in patients with scrub typhus, Ann. New York Acad. Sc. *53*:375–384, Sept. 15, 1950.
21. Bauer, R. E.; Parker, R. T.; Hall, H. E.; Benson, J. F.; Joslin, B. S.; Hightower, J. A.; Snyder, M. J.; Venable, S. J., and Woodward, T. E.: Clinical and experimental observations with terramycin in certain rickettsial and bacterial infections, Ann. New York Acad. Sc. *53*:395–406, Sept. 15, 1950.
22. Montmorency, F. A.; Caffery, E. L., and Musselman, M. M.: Observations on the use of oxytetracycline intramuscularly, Antib. & Chemo. *4*:313–318, Mar., 1954.
23. Brannick, T. L.; Martin, W. J.; Geraci, J. E., and Nichols, D. R.: Intramuscular administration of oxytetracycline and studies of its concentration in the serum, Proc. Staff Meet., Mayo Clin. *29*:183–192, April 7, 1954.
24. Farley, W. J., and Koniecny, L.: Terramycin by subcutaneous clysis, J. Pediat. *42*:177–184, Feb., 1953.
25. Kagan, B. M.; Mendelsohn, R. S.; Miller, R. A., and Elegant, L. D.: Subcutaneous administration of oxytetracycline, Antib. & Chemo. *4*:308–312, Mar. 1954.
26. Blattner, R. J.: Recent therapeutic advances in rickettsial and viral infections, South. M. J. *44*:685–691, 1951.
27. Finland, M.: Antimicrobial treatment for viral and related infections. I. Antibiotic treatment of primary atypical pneumonia, New England J. Med. *247*:317–325, Aug. 28, 1952.
28. Gravel, F. B., and Ball, W. O.: Evaluation of the treatment of primary atypical pneumonia with aureomycin, chloromycetin, and terramycin, J. Pediat. *39*:155–167, Aug., 1951.
29. James, D. G.: Primary atypical pneumonia, J. A. M. A. *151*:810–813, Mar. 7, 1953.
30. Meiklejohn, G.; Thalman, W. G.; Waligora, D. J.; Kempe, C. H., and Lennette, E. H.: Chemotherapy of primary atypical pneumonia, J. A. M. A. *154*:553–557, Feb. 13, 1954.
31. Crump, E. P.: The newer drugs and their indications in childhood, Postgrad. Med. *13*:552–562, June, 1953.
32. Anon.: Antibiotics in whooping cough. [Editorial], Brit. M. J. *2*:769–770, Oct. 3, 1953.
33. Newman, B.; Gavis, G., and Weinberg, S.: Treatment of pertussis with intramuscular oxytetracycline (Terramycin), Antib. & Chemo. *4*:934–938, Sept., 1954.
34. Oehlecker, G.: Über den heutigen Stand der Keuchhustenbehandlung mit Antibiotika, Medizinische *27–28*:916–918, July 11, 1953; abstr. in: Arztl. Praxis, July 23, 1953.

Oxytetracycline in Pediatrics

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In reviewing the use of oxytetracycline (Terramycin*) in pediatric practice as part of this symposium, infectious diseases peculiar to childhood and the problems most commonly associated with them will be stressed. One must be aware of the important and abundant studies in adult patients; however, proper recommendations as to the management of childhood ills must finally come from studies in children. Reference to such studies will be made almost exclusively in this paper; some thoughts of course will stem from personal experience. No attempt will be made to include all of the available literature.

It seems easier to partition this discussion of oxytetracycline into three sections: (1) therapeutic use in the treatment of well-established diseases, (2) prophylactic use in the prevention of infections even though no clear division exists between them, and (3) dosage and administration.

Since the premature and newborn baby needs special consideration, this group will be discussed separately from the infant and child.

THERAPEUTIC USE

The Premature and Newborn Baby

The dangers of the neonatal period are many and the number of deaths associated with infection is high. The natural defensive barriers of the newborn against infection are poor, particularly in the premature. Their reactions have been likened to a test tube; clinical manifestations are absent and only a narrow margin of safety exists. *Escherichia coli* and the staphylococci as well as the streptococci and pneumococci are frequent invaders in this period. Oxytetracycline possesses excellent activity against most strains of these organisms. The initiation of active therapy by an antibiotic, such as oxytetracycline, with a low order of toxicity may rightfully be based on a "knowledgeable intuition" as Platou[1] aptly puts it. Oxytetracycline administered to the expectant mother crosses the placental barrier in good concentration and affords protection to her baby, a factor of importance in infection transmitted to the fetus, such as congenital lues.

Impetigo[2, 3] responds well at any age to the topical application of oxytetracycline ointment, but, in this period when systemic invasion so readily occurs, systemic administration is best. Any inflammation of the umbilicus or the skin about it necessitates immediate therapy, since extension into contiguous abdominal structures or the blood stream may easily develop.

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

Septicemia may occur through other portals of entry. The baby who "just isn't doing well" must be viewed with a high degree of suspicion; the "silent" meningitis, extensive pneumonia, osteomyelitis, or multiple abscesses commonly found at autopsy after a sudden death in the nursery attest to the advisability of early therapy.

No true specific agent is available for epidemic diarrhea of the newborn; the causative agent is undetermined. Neter et al[4, 5] and others[6] have isolated a serotype of *E. coli* from these babies and have noted significant improvement upon administration of oxytetracycline. Certainly the possibility of aid in this devastating disease warrants its use. Active fluid replacement and supportive care of course is mandatory.

The management of other acute, established infections in this age period is basically the same as in the older child. One must, however, bear in mind the relatively more common occurrence of enteric pathogens and the more marked invasiveness of the stubborn coagulase-positive Staphylococcus in the newborn. Good therapy may thus require the combination of streptomycin or one of the newer agents, such as carbomycin,* with oxytetracycline. Earlier erroneous impressions concerning clinical antibiotic antagonism have been dissipated.

THE INFANT AND OLDER CHILD

Respiratory Disease. The greatest amount of antibiotics is undoubtedly used in infections of the respiratory tract. The number of types and strains of organisms present and able to produce symptomatic illness is large. Most of the common gram-positive forms will respond well to penicillin. However, since in many a mixed infection exists or the primary causative agent is gram-negative, such as *Hemophilus influenzae* and *H. pertussis* or occasionally *E. coli* and *Klebsiella pneumoniae*, the need for an antibiotic, such as oxytetracycline, with a broader range of activity is apparent. This is of practical importance in the patient cared for at home without benefit of nose and throat culture; even in the hospital with good laboratory facilities, identification of the responsible organism is often difficult and sensitivity testing confusing.

The so-called "upper respiratory infection" has our undivided attention on sick call throughout most of the year. It is usually a syndrome complex involving the nasopharynx and one or all of its contiguous structures, namely, the ear, sinuses, tonsils, cervical glands, and larynx. Many reports[7, 8, 12, 13] have emphasized the rapid control of acute tonsillitis, sinusitis, beta hemolytic streptococcal pharyngitis, otitis media, and laryngotracheobronchitis with oxytetracycline.

Any involvement of the middle ear demands careful attention; to aim at preventing permanent change and recurrences, high initial dosage and prolonged administration are necessary. The duration of treatment depends on the satisfactory return of the normal drum upon repeated examination. As in all potential "closed space" infections, the antibiotic must make good contact with the microorganisms while the circulation is still unimpaired; if not, paracentesis may be indicated.

Croup may refer to a number of conditions involving the glottis and structures

* The trade name of Chas. Pfizer & Co. for carbomycin is Magnamycin.

above and below it. Whatever the etiology, the immediate and chief concern is the degree of impairment of respiratory exchange. The "spasmodic" type is said to be viral. Any of the respiratory organisms may be involved. Although suggestive lesions, such as a diphtheritic membrane or a cherry-red influenzal epiglottitis, are helpful in determining the etiology, absolute diagnoses must await bacteriologic study. In the meantime, the frequently serious nature of croup demands immediate therapy with an antibiotic, such as oxytetracycline, that will effectively cover all etiologic possibilities. When extension has occurred into the smaller bronchial radicals, as in laryngotracheobronchitis, early therapy may be life saving. Of course, proper humidification, oxygen, and an artificial airway, if necessary, are essential.

Very few children, especially in the younger age group, are now seen with the old-fashioned variety of lobar pneumonia with consolidation and its complications. Diffuse infection of the bronchial tree with varying degrees of parenchymal involvement is common. Bronchopneumonia of bacterial origin responds rapidly to oxytetracycline, and many favorable reports have been received.[9–11, 14, 15] Graves and Ball[16] reported excellent results in a group of 36 children with primary atypical pneumonia. Suitable criteria for diagnosis were obtained. Most investigators consider it a viral disease, since the causative microorganisms have not been determined, and question the efficacy of an antibacterial agent. Acute bronchiolitis in the young infant may have a similar etiology. Since marked respiratory embarrassment is often a prominent feature, it is frequently a serious problem. I have observed good results with subcutaneous oxytetracycline in addition to oxytetracycline by aerosol and the newer surface acting agents.

The successful management of the pulmonary infections in mucoviscidosis or pancreatic fibrosis has been dramatic.[17] Early diagnosis with the aid of better diagnostic methods in the young infant followed by continuous oxytetracycline has changed the outlook for many of these children from one of early mortlaity or chronic invalidism to one of normal growth and development. The effect has been so striking that it has been suggested that oxytetra cycline may have directly enhanced their nutritional balance or metabolic efficiency similar to the effect of oxytetracycline feed supplements in livestock. Coodin,[18] however, in working with normal premature babies demonstrated no such growth stimulus. It now appears that this property is not a growth factor but is secondary to the control of infection or of intestinal bacteria. Nevertheless, since both oxytetracycline and Vitamin B_{12} are products of streptomyces fermentation, one can understand how some interesting speculation as to a nutritional factor has arisen.

Contagious Diseases of Bacterial Origin. The *Streptococcus hemolyticus*, *H. pertussis*, and *Corynebacteria diphtheriae*, as would be expected from in vitro studies, disappear rapidly from the throats of those with scarlet fever,[19] whooping cough,[20] and diphtheria[21] respectively under oxytetracycline therapy. The clinical response of the child with scarlet fever is good and one seldom encounters the immediate complications, such as the otitis that frequently followed this virulent infection. Furthermore, the possibility of preventing subsequent rheumatic fever as well as acute hemorrhagic nephritis exists.

A number of reports[5, 20, 22, 23] on the favorable influence of oxytetracycline in pertussis have appeared. It is difficult to evaluate a therapeutic agent in this variable and relatively protracted illness. Control of the offending organism does not control the disease. However, with the present evidence and from practical experience, oxytetracycline is indicated in full dosage in infants in whom the mortality is highest. These studies emphasize the need for early therapy in suspected cases. Expert nursing care is imperative as always.

Karelitz[21] has had remarkable preliminary success with oxytetracycline in faucial diphtheria and in carriers. Fortunately, at least in the United States with present immunization procedures, the disease is uncommon.

Gastrointestinal Disease. Epidemic diarrhea of the newborn has been discussed under that age group. Any of the enteric pathogens may cause diarrhea in the young child. However, a virus may be suspected when no pathogen is demonstrable. One must always search for a parenteral source of infection, which may be present in an appreciable percentage of cases. In my experience, the ear has been a frequent and often overlooked offender in infancy. With control of the otitis with oxytetracycline, the secondary intestinal disturbance usually subsides.

Oxytetracycline has been shown to have potent activity against most strains of *Shigella* and *Salmonella* in in vitro study. Clinical effectiveness in bacillary dysentery has also been demonstrated in children.[24, 25] Conflicting reports have been received in typhoid fever; the importance of adequate dosage of at least 100 mg./Kg. per day is emphasized as was pointed out earlier by Reilly and Earle.[26]

Pinworm infestation in children reaches astounding proportions throughout the world and is very prevalent in the United States. Wells and his group[27] first found that oxytetracycline was very effective in eradicating the pinworm ovum from the stool of their patients under treatment for yaws. Bumbalo et al[28] more recently found oxytetracycline to be the most effective drug in a comparative study of several common oxyuricides. They obtained an 84 per cent cure rate using a dosage of 10 mg./lb. per day in three divided doses for seven days. The exact mode of action is not known. Oxytetracycline in active form is excreted in large amounts in the feces.

Other Infections. Meningitis is a serious disease requiring expert care. Hoyne[29, 30] and his associates have reported the successful use of oral, intramuscular, and intravenous oxytetracycline in the most common types, namely, meningococcal, *H. influenzae*, and pneumococcal. The intravenous route should always be employed initially. Oxytetracycline diffuses poorly into the cerebrospinal fluid through the normal meninges; Pulaski,[31] however, has pointed out the altered permeability of the inflamed meninges and found good concentration in an adult patient. Cerebral tissue concentration may be of primary consideration. Many reliable investigators have used a variety of methods and therapeutic agents with excellent results. More important perhaps is early and adequate dosage and careful management.

Acute pyelitis is seen commonly in the female child. Bacterial inhabitants of the bowel most frequently invade the urinary tract. High concentrations of active oxytetracycline are found in the urine of children on relatively low dosage. It is recommended, however, that higher dosage be used as in other infections to maintain good tissue levels. This is especially true in recurrent pyuria owing to congenital

malformation with obstruction or stasis. Resistant strains of organisms, such as *Pseudomonas* or *Proteus*, are not infrequently encountered. In no condition is there a necessity for more careful antibiotic therapy or more accurate bacterial sensitivity testing.

Successful management of blood stream infections caused by susceptible organisms has been observed in children.[14, 22] Arnold and Reeves[23] reported a *Streptococcus viridans* endocarditis cured with oxytetracycline. Since oxytetracycline has been demonstrated to be not only bacteriostatic but bactericidal in higher concentrations, intravenous administration should be employed as long as practical. Here, too, laboratory assistance is of real importance in order to select the most effective antibiotic or combination.

Surgery of the infant and small child now holds little fear; great strides have been made in the past decade. Besides improved surgical techniques and pediatric care, not a little of the credit must be given to the protection afforded by the newer antibiotics. Control of the circulation and electrolyte balance during and after operation is essential and intravenous oxytetracycline may be easily given with the necessary fluids. It is particularly indicated for perforation of the appendix or in the repair of congenital or obstructive lesions of the bowel, where the gram-negative bacteria of the intestinal flora may be troublesome.

The rickettsial diseases will be covered in another portion of this symposium. Early successes with oxytetracycline in the treatment of rickettsialpox and Rocky Mountain spotted fever in children were cited by Bauer et al,[24] Schoenback et al,[25] and Rose.[26] Similar response has been observed in typhus, Q fever, and other diseases caused by these microorganisms.

PROPHYLACTIC USE

A discussion on the use of antibiotic agents in the protection of the patient from "secondary" bacterial infection that will adversely influence the course of the primary illness or cause new and sometimes more serious morbidity is open to justified scrutiny. Controlled clinical information and valid statistical data are not easy to acquire. In general, true prophylactic therapy against infectious disease is as important a consideration as any other form of preventive care in infancy and childhood.

THE PREMATURE AND NEWBORN BABY

In the newborn period, the method of Crede for the prophylaxis of ophthalmia neonatorum using silver nitrate has been supplanted in many institutions by an antibiotic, usually penicillin because of the potential hazards and higher incidence of chemical conjunctivitis with the former method. The possibility of a mixed infection and of inclusion blennorrhea makes the stable oxytetracycline ointment a sensible choice of antibiotic preparation. Inclusion blennorrhea has been treated successfully by Thygeson.[27] Willcockson and Cox[28] have reported on their satisfactory experience with oxytetracycline ointment for such prophylaxis.

The susceptibility of infection of the newborn has been previously stated. The indications for routine protective therapy, however, should be based on known

potential hazards, such as the condition of the baby, the circumstances of delivery, infection in the mother or nursery contacts, or poor nursery facilities or techniques. In spite of much speculation regarding the overgrowth of resistant microorganisms, there has been no convincing evidence of danger of long-term oxytetracycline therapy given under proper medical supervision and observation. Coodin[15] found no untoward effects and no differences compared to a similar number of controls in the continuous daily administration of 25 mg. of oxytetracycline to a large series of premature infants. The incidence of bacterial and monilial infection was very low in both groups. Therapeutic blood serum levels were demonstrable on periodic sampling. The staphylococci were a more frequent inhabitant of the nasopharynx in the treated babies. Shwachman and his group[17] found this organism in their children with mucoviscidosis but could ascribe no symptomatology to it. One must still be mindful of the serious potentialities of this organism as pointed out by Finland et al[39] and others,[40, 41] but it does not necessarily forebode evil.

Respiratory disturbances, such as incomplete or delayed expansion of the lungs, aspiration of amniotic fluid or mucous plugs, and hyaline membrane disease, are common in the premature and full-term newborn. As pulmonary infection may frequently follow these conditions, early oxytetracycline therapy in adequate dosage is warranted. Adequate protection also may be indicated in the baby with erythroblastosis fetalis who is subjected to replacement transfusion, especially when given through the umbilical vein.

THE INFANT AND OLDER CHILD

The question of the "indiscriminate" use of antibiotics in respiratory illnesses of supposedly viral origin often arises. It is not my intention to condone such practice. However, on a night call when confronted with a truly toxic child with high fever in the presence of anxious parents, one's good clinical judgment may be severely taxed. One wonders how serious an error this may be in view of the declining incidence of bacterial pneumonia, meningitis, chronic otitis and mastoiditis, and other acute infectious diseases. One is also mindful of the work of Wannamaker et al[42] and Denny et al[43] regarding the prevention of rheumatic fever by using antibiotics to achieve the eradication of the hemolytic streptococci from the throats of patients with streptococcal pharyngitis.

Influenza-like outbreaks may "lose their punch" with the control of secondary complications. Such complications in the great influenza epidemics were so prevalent as to be considered part of the natural course of the disease and to a great extent the cause of the striking mortality. A type of synergism between the virus and the bacterial organisms has been suggested.

Among the contagious diseases similar safeguards are needed to prevent otitis media and bronchopneumonia following measles, as well as aspiration pneumonia in bulbar and respiratory poliomyelitis. Children undergoing tonsillectomy or tooth extraction deserve the protection of antibiotic prophylaxis particularly if they are suspected of having had rheumatic fever. The bacterial flora of the nasopharynx will be appreciably reduced and the hemolytic streptococci eliminated with oxytetracy-

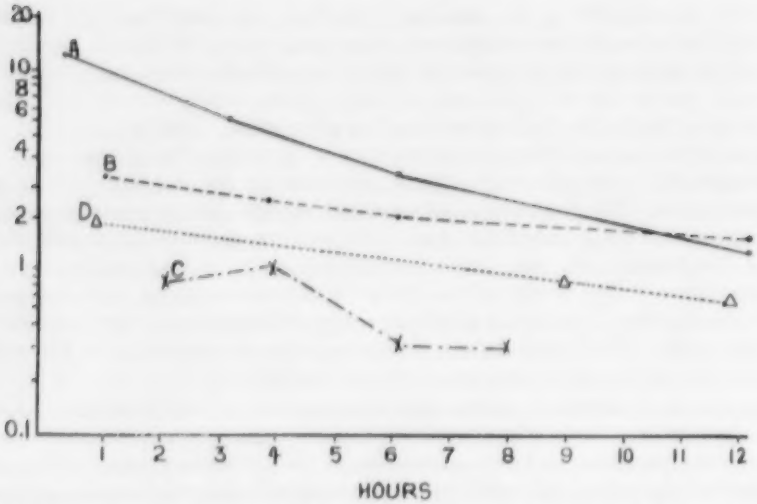

FIG. 1. Comparative mean serum levels of single doses of oxytetracycline. Type of administration: A, intravenous (6.6 mg./Kg.);[46] B, subcutaneous (10 mg./Kg.);[16] C, oral (11 mg./Kg.);[46] D, intramuscular (6 mg./Kg.).[14]

cline. Studies are now underway in the evaluation of oxytetracycline for the prevention of recurrences of the active rheumatic state. An adequate oxytetracycline "umbrella" is also indicated in the surgical repair of congenital cardiac lesions in children.

Oxytetracycline has significantly reduced the number of severe intercurrent infections with nephrosis. Metcoff[44] has recently cited Cooke's work[45] in New Haven with a controlled group of children using continuous dosage of 20 to 25 mg./Kg. per day. Similar prolonged administration as employed in mucoviscidosis, bronchiectasis, and congenital urinary disorders might also be considered prophylactic.

The child with altered defense mechanisms and resistance as in leukemia or under intensive treatment with the newer hormones may be a candidate for prophylactic oxytetracycline.

DOSAGE AND ADMINISTRATION

Data on the absorption and distribution of oxytetracycline in children via the oral, intramuscular, subcutaneous, and intravenous routes are available through the studies of Hunt et al,[46] O'Regan and Schwarzer,[14] and Farley and Konieczny.[15] Comparative blood serum levels following single doses of oxytetracycline using these modes of administration are compiled in the composite chart in figure 1. If one knows the relative in vitro inhibitory concentrations of the antibiotics against most of the commonly encountered bacteria, one can thus use this information to aid in establishing preliminary dosage regimens that subsequently must be subject to suc-

cessful clinical trial. Such a working guide is recommended in the suggested dosage guide in table I.

Special oral preparations are available for children. The more insoluble amphoteric form of oxytetracycline is utilized in a readily accepted raspberry-flavored vehicle. The soluble 50 mg. tablets can be used through an indwelling polyethylene tube in premature infants.

Intramuscular oxytetracycline has only relatively recently been released for general use. It is valuable when other routes are not feasible. Good techniques, to prevent subcutaneous injection, and close observation are necessary, since otherwise local reactions may occur. I have found that it is better tolerated and more satisfactory in infants to whom relatively larger doses may be given at 12 hour intervals.

The buffered intravenous oxytetracycline hydrochloride by subcutaneous clysis has proved to be very useful and practical. High dosage can be conveniently and safely given. Platou[1] has used it very successfully in his premature and newborn nursery. Kagan et al[17] has also confirmed our studies.[15] All types of fluids and electrolyte solutions can be used except those containing calcium and protein hydrolysate, as precipitation may occur. Hyaluronidase may be used if desired.

TABLE I

Suggested Dosage Guide

Route	Dose mg./Kg.	Interval, hourly	Injected Dilution mg./ml.
Oral	5–20	6	—
Subcutaneous	10–20	12	1
Intramuscular	5–10	12	50–100
Intravenous	5–10	12	5 or less

No comments are necessary in regard to the intravenous route except that, to minimize irritation of the vein during continuous fluid therapy in children, small volumes of diluent should be used at the usual concentration of 1 to 5 mg./ml. and dripped in as rapidly as the circulation permits. I prefer this technique to the slower administration that is generally recommended.

Oxytetracycline by aerosol is used with 75 per cent propylene glycol at a concentration of 50 mg./ml. I have been unable to detect the antibiotic in the blood serum of infants given 100 mg. in this fashion under a small plastic hood. In acute respiratory infections it should be used only with systemic therapy.

Rectal administration is mentioned only to be condemned. I have found no detectable oxytetracycline in the serum following oxytetracycline in an adequate dosage by way of punctured capsules or enema. Herrell et al[12] and Hunt et al[16] reported similar experience.

In conclusion, although oxytetracycline is versatile and life-saving ammunition, one must consider it, as any antibiotic or therapeutic agent, solely as a valuable adjunct to competent management of the infections of childhood. Each case should be evaluated on its own without recourse to dogmatic "antibiotic of choice" tables.

Instead, good basic principles must govern one's therapy. Factors to be always kept in mind are:

1. The usual sensitivity of the pathogens commonly found in the particular types of infections.

2. The dosage, duration, and mode of administration required to contact adequately the bacteria and control the infection.

3. The natural resistance and condition of the child.

4. The possibility of a change of bacterial flora under therapy.

5. An awareness of the possibility of hypersensitivity or other untoward reaction.

BIBLIOGRAPHY

1. Platou, R. V.: Presentation before the Post Graduate Course for Physicians and Hospital Administrators, Univ. of Colorado Medical Center, Denver, Mar. 24, 1954.
2. Wright, C. S., and Tichan, D. W.: Local oxytetracycline ("Terramycin") therapy of skin infections, A. M. A. Arch. Dermat. & Syph. *67*:125, Feb., 1953.
3. Reiss, F.: Terramycin in the treatment of skin diseases, New York State J. Med. *52*:1031, April 15, 1952.
4. Neter, E.; Webb, C. R.; Shumway, C. N., and Murdock, M. R.: Study on etiology, epidemiology, and antibiotic therapy of infantile diarrhea, with particular reference to certain serotypes of *Escherichia coli*, Am. J. Pub. Health *41*:1490, Dec., 1951.
5. Neter, E., and Webb, C. R.: Study on etiological role of certain serotypes of *Escherichia coli* and effect of antibiotic therapy in infantile diarrhea, Exper. Med. & Surg. *9*:385, 1951.
6. Shanks, R. A., and Studzinski, L. P.: *Bact. coli* in infantile diarrhea, Brit. M. J. *2*:119, July 19, 1952.
7. Potterfield, T. G., and Starkweather, G. A.: Clinical observations on terramycin in pediatric infections, J. Philadelphia Gen. Hosp. *2*:6, Jan., 1951.
8. Sayer, R. J.; Michel, J. C.; Moll, F. C., and Kirby, W. M. M.: Terramycin: clinical, pharmocologic, and bacteriologic studies, Am. J. M. Sc. *221*:256, Mar., 1951.
9. Woodino, C. H., Jr., and Scott, R. B.: Terramycin in treatment of pneumonias of childhood; a report of ten cases, J. Pediat. *38*:423, April, 1951.
10. Swift, P. N.: Terramycin in the treatment of pneumonia in children, Proc. Roy. Soc. Med. *44*:1066, Dec., 1951.
11. Wolman, B., and Holzel, A.: Terramycin in infections in infants and children, Brit. M. J. *1*:419, 1952.
12. Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Some bacteriologic, pharmacologic, and clinical observations on terramycin, Ann. New York Acad. Sc. *53*:448, 1950.
13. Caldwell, E. R., Jr.; Spies, H. W.; Wolf, C. K.; Lepper, M. H.; Wheldon, R. L., and Dowling, H. F.: Use of terramycin in some infectious diseases. [Abstr.], Am. J. Med. *10*:238, Feb., 1951.
14. O'Regan, C., and Schwarzer, S.: Intramuscular Terramycin: laboratory and clinical studies in children, J. Pediat. *44*:172, 1954.
15. Farley, W. J., and Koniberny, L.: Terramycin by subcutaneous clysis, J. Pediat. *42*:177, Feb., 1953.
16. Graves, F. B., and Ball, W. O.: Evaluation of the treatment of primary atypical pneumonia with aureomycin, chloromycetin, and terramycin, J. Pediat. *39*:155, Aug., 1951.
17. Shwachman, H.; Silverman, B. K.; Patterson, P. R., and Zbeutlin, L. J.: Antibiotics in treatment of pancreatic fibrosis, with emphasis on terramycin, J. A. M. A. *149*:1101, July 19, 1952.
18. Coodin, F. J.: Studies of Terramycin in premature infants, Pediatrics *12*:652, Dec., 1953.
19. Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., and Spies, H. W.: Terramycin in the treatment of pneumococcic and other bacterial infections, Ann. New York Acad. Sc. *53*:433, Sept. 15, 1950.
20. Hazen, L. N.; Jackson, G. G.; Chang, S.-M.; Place, E. H., and Finland, M.: Antibiotic treatment of pertussis; comparison of penicillin, aureomycin, chloramphenicol, and terramycin in 150 cases, J. Pediat. *39*:1, July, 1951.

21. Karelitz, S.: Paper before Meeting of the Philadelphia Pediatric Society, Feb. 10, 1953.
22. Booher, C. E.; Farrell, J. B., and West, E. J.: Pertussis: clinical comparison of the newer antibiotics, J. Pediat. *38*:411, April, 1951.
23. Boodan, A.: Terramycin in pertussis, Brit. M. J. 2:1186, Nov. 29, 1952.
24. Kunstadter, R. M.; Milzer, A., and Kagan, B. M.: Chloramphenicol and terramycin in the treatment of Salmonella and Shigella infections, J. Pediat. *39*:687, Dec., 1951.
25. Pathy, M. S.: Terramycin in salmonella infections, Lancet *1*:196, 1953.
26. Reilly, W. A., and Earle, A. M.: Treatment of typhoid fever with terramycin, J. Pediat. *38*:428, 1951.
27. Wells, H. S.; Shookhoff, H. B.; Mullin, W. G.; Sterman, M. M.; Loughlin, E. H., and Rappaport, I.: Terramycin HCl in the treatment of human pinworm infections, Antib. & Chemo. *1*:299, Aug., 1951.
28. Bumbalo, T. S.; Gustina, F. J.; Bona, J., and Oleksiak, R. E.: Pinworm infection (enterobiasis) in children; a comparative study of four oxyuricides, A. M. A. Am. J. Dis. Child. *86*:592, Nov., 1953.
29. Hoyne, A. L., and Riff, E. R.: Terramycin therapy for meningitis; a report of fourteen recoveries without other medication, J. Pediat. *39*:151, 1951.
30. Hoyne, A. L., and Simon, D. L.: Intramuscular terramycin in treatment of meningitis; report of 21 recoveries, Arch. Pediat. *70*:319, 1953.
31. Pulaski, E. J.; Artz, C. P., and Reis, E.: Terramycin and aureomycin in surgical infections; report of two hundred cases, J. A. M. A. *149*:35, 1952.
32. Scott, R. B., and Woodino, C. H., Jr.: Terramycin hydrochloride in the treatment of Salmonella choleraesus bacteremia, Pediatrics *7*:349, Mar., 1951.
33. Arnold, W. P., Jr., and Reeves, R. L.: Terramycin in the treatment of subacute bacterial endocarditis; case report, Antib. & Chemo. *1*:181, June, 1951.
34. Bauer, R. E.; Parker, R. T.; Hall, H. E.; Benson, J. F.; Joslin, B. S.; Hightower, J. A.; Snyder, M. J.; Venable, S. J., and Woodward, T. E.: Clinical and experimental observations with terramycin in certain rickettsial and bacterial infections, Ann. New York Acad. Sc. *51*:395, Sept. 15, 1950.
35. Schoenbach, E. B.; Beyer, M. S., and Long, P. H.: The pharmacology of terramycin in animals and man with reference to its clinical trial, Ann. New York Acad. Sc. *51*:245, 1950.
36. Rose, H. M.: The treatment of rickettsialpox with antibiotics, Ann. New York Acad. Sc. *55*:1019, Dec. 30, 1952.
37. Thygeson, P.: Terramycin in ocular infections, Tr. Am. Ophth. Soc. *49*:185, 1952.
38. Willcockson, T. H., and Cox, C. D.: Bacteriological studies in newborns using Terramycin, Terramycin-Polymyxin-B and silver nitrate, South Dakota M. J. *6*:147, 1953.
39. Finland, M.; Grigsby, M. E., and Haight, T. H.: Efficacy and toxicity of oxytetracycline (Terramycin) and chlortetracycline (Aureomycin); with special reference to use of doses of 250 mg. every four to six hours and to occurrence of staphylococcic diarrhea, A. M. A. Arch. Int. Med. *93*:23, Jan., 1954.
40. Hay, P., and McKenzie, P.: Side-effects of oxytetracycline therapy, Lancet *1*:945, 1954.
41. Cramer, R., and Rossi, E.: Über Brechdurch fälle mit fatalem Kreislaufkollaps bei Kindern nach Chloromycetin- und Terramycinmedikation; Diskussion über die Staphylokokkenenteritis, Helvet. paediat. acta *8*:544, 1953.
42. Wannamaker, L. W.; Rammelkamp, C. H., Jr.; Denny, F. W.; Brink, W. R.; Houser, H. B.; Hahn, E. O., and Dingle, J. H.: Prophylaxis of acute rheumatic fever; by treatment of the preceding streptococcal infection with various amounts of depot penicillin, Am. J. Med. *10*:673, 1951.
43. Denny, F. W.; Wannamaker, L. W., and Hahn, E. O.: Comparative effects of penicillin, aureomycin, and terramycin on streptococcal tonsillitis and pharyngitis, Pediatrics *11*:7, Jan., 1953.
44. Metcoff, J.: Area 1 Meeting, Amer. Acad. Pediatrics, Boston, April 20, 1953.
45. Cooke, R. E.: Nephrotic syndrome in children, Connecticut M. J. *17*:988, 1953.
46. Hunt, A. D., Jr.; Kelley, R. S.; Coriell, L. L.; Murphy, M. L.; Tashman, S. G., and Stevens, G.: Studies on absorption and distribution of terramycin in children, Pediatrics *9*:607, 1952.
47. Kagan, B. M.; Mendelsohn, R. S.; Miller, R. A., and Elegant, L. D.: Subcutaneous administration of oxytetracycline, Antib. & Chemo. *4*:308, 1954.

Oxytetracycline in Tropical Medicine

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During the past century, tropical medicine has emerged from the shadowy vale of superstition and fantasy in which diseases were believed to be caused by miasmas, curses, black magic, or possession by devils, and in which their treatment corresponded to their imaginary origins. Cinchona bark and ipecacuanha were given in malarial fevers and dysenteries for more than 200 years before plasmodia and *Endamoeba histolytica* were discovered and related to their respective diseases. Except for these, many years and even decades usually have elapsed between the discovery of the etiological agent for a disease and the application of rational and effective therapy for that disease.

In the early part of the twentieth century, it was not a simple matter to convince doctors in the tropics that many of the remedies used to treat diseases in temperate climates could be applied to those of the tropics, particularly if they persisted in clinging to antiquated notions about the etiology of these diseases. This inflexible attitude concerning the scourges that have afflicted mankind for countless centuries was overcome when, during World War II, it was realized that the armamenta then currently available for combatting these diseases were woefully inadequate.

When this startling realization fully registered, it jolted both military and civilian medicine from its stagnant apathy. Campaigns were launched to control or prevent tropical infections and programs were inaugurated to find and develop new specific therapies for them. In some regions, these control campaigns have been successful against certain diseases and their agents. However, in others control programs hastily and empirically conceived, some of limited scope, only temporarily blunted the severity of these diseases. It was soon recognized that many of the problems of control and prevention should have been considered in their broader aspects, including traditional, sociological, and medical aspects.

The advent of the sulfonamides ushered in a new but comparatively brief era of specialized chemotherapy in tropical medicine. Sadly, it was discovered that the sulfonamides were without effect on the causative agents of many infections, while in others, which at first were highly susceptible, a new and almost total drug resistance developed. The sulfonamides were succeeded by penicillin and streptomycin, and these in turn by the broad-spectrum antibiotics, which have afforded almost limitless possibilities of specific therapy in tropical medicine as well as efficient means for the control and prevention of many tropical diseases.

Upon reviewing the history of specific therapy in tropical infections, it is plainly evident that the antibiotics encountered considerably less resistance in their application to these diseases than some of their predecessors. Undoubtedly, the manner in which these miracle medicines were proclaimed accounted to a large degree for

their rapid acceptance in the treatment of tropical diseases. On the other hand, their reception has been so enthusiastic in some places that infections, which from laboratory studies could not have been expected to respond, were treated and reported adversely. Fortunately, only a few tropical infections have later shown resistance to antibiotics under circumstances in which they previously had been susceptible.

As a consequence of critically reviewing reports on the efficacy of broad-spectrum antibiotics and chemotherapeutic agents commonly used in tropical medicine and, considering the results of our own laboratory and clinical investigations, we currently offer the opinion that if only one drug could be selected to take to the tropics that drug should be oxytetracycline.* We believe that the evidence from the reports of investigators in special fields of tropical medicine, *ut infra*, will justify this view.

OXYTETRACYCLINE IN PROTOZOAN DISEASES

Amebiasis. Since the discovery of *E. histolytica* in the feces of a Russian peasant by Losch in St. Petersburg in 1873 and the linking of this amoeba to dysentery by Koch and Gaffky in 1887, many remedies including the bicentennial ipecacuanha, its alkaloid, emetine, discovered by Rogers in 1912, the arsenicals, the halogenated quinolines, and recently the antibiotics have been used to treat amebiasis. With the arrival of amost every amebacide, there is usually an early enthusiasm for its singular clinical efficacy. However, these illusions later are dispelled when opinions regarding their efficacy are reversed. After more critical evaluation many drugs are discarded as valueless, while others are assigned to roles of adjunctive amebacides.

The criteria on which cure or successful treatment of acute amoebic dysentery and chronic intestinal amebiasis are based have not been uniform. In some reports, posttreatment follow-up has been too brief to permit an adequate evaluation of the amebacide, cure being reported as early as 20 days, while in others the posttreatment follow-up has extended from six weeks to three months or more. In some reports, the diagnosis of infection with *E. histolytica* obviously was not confirmed by examination of iron-hematoxylin stained fixed fecal smears. In most reports, little attention has been directed toward environmental factors and the minimum period during which individuals possibly can become reinfected. Some reports deal with the results of treatment of acute amoebic dysentery; some with the efficacy of amebacides in series of cases that are mixed or are predominantly acute or chronic; while still others limit their data to results of treatment of chronic intestinal amebiasis. Attention has been focused lately on the variable responses of different strains of *E. histolytica* in vitro to the same amebacide.

Acute Amoebic Dysentery. Undoubtedly, the most carefully evaluated and extensive series of cases of acute amoebic dysentery in which oxytetracycline, standard amebacides, and two other broad-spectrum antibiotics, chlortetracycline (Aureomy-

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

cin*) and chloramphenicol, were tested is that of the Joint Dysentery Unit operating in South Korea.[1] In this series of 538 cases, 104 were treated with oxytetracycline alone; 97 were treated with oxytetracycline combined with standard amebacides; and 22 with oxytetracycline combined with chloroquine.

After the diagnosis of acute amoebic dysentery had been established, an initial loading dose of 2 Gm. of oxytetracycline was given orally, followed by 0.5 Gm. every six hours for 10 days. Specimens of feces were examined microscopically for *E. histolytica* on the first, second, fourth, and sixth posttreatment days, and once weekly thereafter for periods of six weeks after starting treatment. Criteria of cure or successful treatment were: absence of diarrhea and significant symptoms of enteric disorder; absence of exudate and *E. histolytica* trophozoites or cysts in the feces; and finally on weekly posttreatment sigmoidoscopic examinations, no evidence of colitis. Treatment was recorded as successful when all of these conditions were maintained during the period of six weeks after commencing amebacidal therapy.

Of the 104 cases treated with oxytetracycline alone, 94.2 per cent were considered, according to the previously mentioned criteria, to be cured. Chlortetracycline produced cures in 75.4 per cent of the cases; while chloramphenicol effected only 29.6 per cent cures. The best single standard amebacide produced only 50 per cent cures, and a combination of three standard amebacides raised the percentage of cures to 83 in 23 cases. The administration of a combination of oxytetracycline and a standard amebacide in 97 cases produced almost 96 per cent cures, while a combination of oxytetracycline and chloroquine was successful in 20 of 22 cases (91 per cent).

As a result of these unmistakably favorable results, the members of the unit regarded oxytetracycline as the most effective therapeutic agent in acute amoebic dysentery.

Other investigators, who have treated acute amoebic dysentery with oxytetracycline and compared its efficacy with that of other antibiotics and standard amebacides, have obtained results similar to those claimed by the Joint Dysentery Unit.[2–4]

Chronic Amebiasis. Possibly the largest series of cases of chronic intestinal amebiasis treated with oxytetracycline are those reported by Most and Van Assendelft,[5] and by Tobie et al.[6] Most and Van Assendelft stated that oxytetracycline in daily doses usually of 2 Gm. given for 10 days, effected cure of almost 90 per cent of 65 patients with chronic colonic amebiasis. They did point to the fact, however, that this series included 21 cases that were observed posttreatment for 30 days or less, and that instead of only 10 per cent relapses noted at that time, the relapse rate conceivably might rise to 15 or 20 per cent when these cases were followed for longer periods. Tobie et al, reporting on the results of a mass treatment trial with oxytetracycline in a state school, found that daily oral doses of 1 to 2 Gm. of this antibiotic administered simultaneously for 10 days to 222 individuals reduced the prevalence

* The trade name of Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline is Aureomycin.

rate from 49 per cent at the commencement of the experiment to 1 per cent at the end of six months. The implications of the results of these two studies are manifestly disparate.

In a series of 42 cases of chronic intestinal amebiasis treated with 2 Gm. of oxytetracycline daily for 10 days, using as criteria of successful treatment specimens of feces consistently negative for cysts of *E. histolytica* when examined by concentration techniques at two, four, and six days, and weekly through a minimum of six weeks' posttreatment, we obtained less impressive results with cures calculated at a little more than 70 per cent.[7]

Although the results reported by various investigators concerning the treatment of chronic intestinal amebiasis have differed, the majority agree that oxytetracycline is the most efficacious single antibiotic.[7–11]

Hepatic Amebiasis. The reported results of treatment of hepatic amebiasis, amoebic hepatitis and amoebic liver abscess, have been contradictory. In the series of cases of acute amoebic dysentery reported by the Joint Dysentery Unit, 1 of the 104 patients treated with oxytetracycline alone developed an amoebic hepatitis. Of the 7 patients reported by Killough and Magill,[3] 1 patient developed a hepatic abscess during treatment with oxytetracycline. Contrariwise, Charmot and Le Henand used oxytetracycline in treating 10 cases of amoebic hepatitis.[12] Six patients, observed for two to six months, were considered as cured. Four patients did not respond "as hoped for" and after four to six days were treated with other drugs.

The consensus of expert opinion is that oxytetracycline and other antibiotics have uncertain value in the treatment of hepatic amebiasis.

Balantidiasis. Infection with the ciliate, *Balantidium coli*, although uncommon, may be manifested either as a mild colitis, an acute dysentery, or as a carrier state. Neghme et al[13] noted good results with the use of oxytetracycline in the treatment of balantidiasis, and Weinstein et al[14] reported the successful treatment of a case of balantidial dysentery with oxytetracycline. Hoekenga[15] used oxytetracycline in dosages of 0.75 to 2 Gm. daily for 10 days to treat 10 patients ranging in ages from 6 to 40 years. During a three to five month posttreatment period, 6 to 14 fecal specimens per patient having been examined for *B. coli*, only 1 patient relapsed at three months.

Giardiasis. We have observed no effect by oxytetracycline or other broad-spectrum antibiotics on infections with the flagellate, *Giardia lamblia*.[16] We are not cognizant of any reports on the successful treatment of giardiasis with any antibiotic.

Malaria. Although oxytetracycline, chlortetracycline, and chloramphenicol have exhibited some activity against the plasmodia of bird malaria, these antibiotics only have been therapeutically active when given in exceptionally large doses in human malaria.[17] RuizSanchez et al[18, 19] reported the treatment of 13 cases of *Plasmodium vivax* and 4 cases of *Plasmodium falciparum* malaria with oxytetracycline in doses of 35 to 222 mg./Kg. daily for 6 to 10 days. Although these authors stated that all cases responded favorably to treatment with oxytetracycline, the asexual parasites were slow to disappear, three to nine days, and the gametocytes of *P. falciparum* persisted. Using doses of 2 Gm. of oxytetracycline daily for five days to treat yaws,

and for 7 to 10 days in the treatment of amebiasis and certain helminthiases, we observed no effect by this antibiotic on *P. falciparum* malaria.[20] As a matter of fact, we observed relapses of *P. falciparum* malaria occurring within a few days after these oxytetracycline dosages. From these results and the extremely large doses required to effectuate the disappearance of asexual parasites, it is apparent that this antibiotic has no place in the therapy of malaria.

Other Protozoan Diseases. We are not aware of any authentic reports concerning the effective treatment with oxytetracycline of toxoplasmosis, and any of the forms of leishmaniasis and trypanosomiasis.

OXYTETRACYCLINE IN HELMINTHIASES

Intestinal Helminthiases: Ascariasis, Hookworm, and Trichuriasis. Investigations to determine the effect of oxytetracycline on certain intestinal helminths were stimulated by personal observations that, during the treatment of yaws with this antibiotic,[13] those patients with concurrent ascariasis expelled many of their ascarids. Subsequently it was shown that oxytetracycline administered orally to mice also had a significant suppressive effect on the mouse pinworm, *Aspiculuris tetraptera*.[21]

As a result of the aforementioned observations on human ascariasis, we proceeded to determine quantitatively, by means of dilution egg counting of the feces, the effect of orally administered oxytetracycline on *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*. We found that this antibiotic, administered daily for 10 days, markedly reduced the egg counts in each helminthiasis. We considered this result to have been caused partly by some worms having been expelled, particularly *Ascaris*, and partly by the suppressive effect of this antibiotic on the reproductive activity of the worms. At the end of a four week posttreatment period, egg counts had risen appreciably from immediate posttreatment levels but had not approached pretreatment levels. These effects, however, were not of sufficient magnitude to be considered efficient treatment for ascariasis, hookworm, or trichuriasis.[22]

Enterobiasis. The results of treating *Enterobius vermicularis*, pinworm, infections with oxytetracycline are markedly different from those obtained in the aforementioned helminthiases and match the effects of this antibiotic on mouse pinworm. In 1951, we reported the successful treatment with oxytetracycline base of 30 cases of enterobiasis in Haiti.[23] In a recent article,[24] we described successful therapy with crystalline oxytetracycline in 88 of 92 cases of enterobiasis, using as criteria of cure Scotch-tape impressions that were consistently negative for *Enterobius* eggs during a 35 day posttreatment period. This posttreatment follow-up exceeded by periods of up to 21 days those used in deciding that 85 per cent of cases treated with piperazines were cured, and on the basis of which oxytetracycline would have been 100 per cent instead of 95 per cent effective. We have not altered our original opinion that oxytetracycline, given for seven days in doses of 1 Gm. daily to children less than 5 years old; 1.5 Gm. daily to children between 5 and 10 years old; and 2 Gm. daily to those more than 10 years old and to adults, is currently the most efficient single anthelmintic in enterobiasis.

Shigellosis. Earlier expectations that sulfonamides would continue as highly effective therapeutic agents in shigellosis have not been fulfilled. Since the sulfonamides were first used in the treatment of bacillary dysentery, many strains of *Shigellae* have become resistant to them. In a recent study, Hardy, Mason, and Martin[25] of the Joint Dysentery Unit in Korea found that of 225 isolations of *Shigella*, 60 per cent were resistant to sulfadiazine in vitro. Contrariwise, only 0.4 per cent were resistant to oxytetracycline, with 1 per cent exhibiting moderate sensitivity; 2 per cent were resistant to chloramphenicol, with 17 per cent moderately sensitive; and 10 per cent were resistant to chlortetracycline, with 24 per cent moderately sensitive.

The results of these in vitro studies were matched by the clinical responses. At the end of 24 hours of treatment, 68 per cent of the cases treated with oxytetracycline had changed from culturally positive to negative; while 67 per cent treated with chloramphenicol, 56 per cent treated with chlortetracycline, and only 10 per cent receiving sulfadiazine had become culturally negative. From the second through the seventh day after commencing therapy, the percentage of persistently negative cultures rose to 98 in cases treated with oxytetracycline, with chlortetracycline closely paralleling oxytetracycline, and chloramphenicol being slower and less favorable during the same period. By the seventh day, sulfadiazine had effectuated only 60 per cent persistently negative cultures.

Since neither chlortetracycline nor chloramphenicol surpassed oxytetracycline in clinical bacteriologic responses, Hardy, Mason, and Martin preferred oxytetracycline in the treatment of bacillary dysentery for the following reasons: almost all *Shigellae* were found by in vitro testing to be highly sensitive to it. Oxytetracycline produced no troublesome side reactions in these patients. Inasmuch as problems of differential diagnosis arise in areas in which amoebic and bacillary dysentery both occur and since oxytetracycline is far superior to chlortetracycline and chloramphenicol in the treatment of acute amoebic dysentery, it is advisable to use the antibiotic with the broadest coverage, i.e., oxytetracycline.

Plague. The experimental treatment of plague has kept pace with the discovery of each new antibacterial agent. The finding that penicillin was ineffectual against *Pasteurella pestis* merely led to further investigations with streptomycin and then the broad-spectrum antibiotics as they were developed.[26]

When in vitro and in vivo studies indicated a good antibacterial effect, they were followed shortly by clinical testing. For several years, streptomycin continued to be the preferred therapeutic agent. Further clinical trials with the broad-spectrum antibiotics, although still few in number, have indicated that they are at least as good as streptomycin and can easily be given orally in moderately severe cases. Some investigators who had preferred streptomycin as the antibacterial agent to be used in treating plague, lately have considered oxytetracycline and chloramphenicol preferable to streptomycin in the treatment of pneumonic plague.[27] The broad-spectrum antibiotics, including oxytetracycline have been used in other forms of plague with similar success.[28,29] The fact that oxytetracycline in large doses protects mice against the lethal component of the toxin of *Pasteurella pestis*[30] suggests that it

might be preferred to chloramphenicol, which exhibits only slight antitoxic activity.

Cholera. Oxytetracycline has been shown to be highly effective in inhibiting 99 of 100 strains of *Vibrio comma* in vitro;[31] while streptomycin, bacitracin, chlortetracycline, and chloramphenicol inhibited no more than 20 per cent of the strains. In mice and monkeys infected with *V. comma*, oxytetracycline provided cures that matched the results of in vitro studies.

Although these results would seem to indicate that the clinical treatment of cholera in humans with oxytetracycline should be highly effective, Das et al[32] reported that cases treated with it had a mortality rate of 11.6 per cent as compared with a control mortality of 18.3 per cent. When the mortality rates were analyzed according to duration of illness before institution of therapy, those cases treated with oxytetracycline within six hours after onset still had a mortality rate of 4.3 per cent against the controls' 8.5 per cent; cases treated within 6 to 12 hours after onset had a mortality rate of 20.3 per cent compared with the control mortality rate of 30 per cent. In another series, Das et al[33] treated 20 cases with intravenously administered oxytetracycline, 16 cases serving as controls. They were of the opinion that oxytetracycline did not provide a significant statistical improvement in mortality rate over that for the control cases.

MISCELLANEOUS BACTERIAL AND VIRAL INFECTIONS

Granuloma Inguinale (Donovanosis). Granuloma inguinale (granuloma venereum) is a chronic infectious disease caused by a gram-negative bacterium, *Donovania granulomatosis*. It is manifested by ulcerous, granulomatous, and scarred lesions, usually of the genital area, and by the presence of characteristic Donovan bodies in pathognomonic large mononuclear cells, which distinguish it from the late stage of lymphopathia venerea.

Oxytetracycline has been used successfully in the treatment of granuloma inguinale by Whitaker et al,[34] and by Wright et al.[35] More recently, Greenblatt[36] reported the successful treatment of 36 cases of granuloma inguinale. Twenty-seven patients were healed either at the termination of therapy or at the time of later examinations made up to 12 months' posttreatment; 9 patients failed to return for follow-upexaminations; 2 patients requiring retreatment responded satisfactorily; there were no known therapeutic failures. Streptomycin and chlortetracycline failed to halt the progress of extensive lesions of a woman observed by us. After changing the antibiotic used to oxytetracycline, the lesions responded satisfactorily with healing[20]. The recommended dosage of oxytetracycline for the treatment of granuloma inguinale is 2 Gm. daily in divided doses for 10 days, as a rule.

Lymphopathia Venerea. Lymphopathia venerea (climatic bubo), a tropical venereal disease occasionally encountered in temperate regions, is caused by a filterable virus and may be manifested in three stages: (1) a transitory primary lesion that is rarely seen; (2) early secondary unilateral or bilateral inguinal or intrapelvic nonsuppurative or suppurative lymphadenitis and periadenitis; and (3) late tertiary chronic granulomatous inflammation of the external and intrapelvic genitalia and rectum resulting in elephantiasis, strictures, pelvic abscesses, and fistulae. At times systemic

extragenital manifestations of lymphopathia venerea occur in the form of meningoencephalitis, uveitis, atypical pneumonia, pleurisy, peritonitis, and arthritis.

Oxytetracycline, chlortetracycline, and chloramphenicol have been tested clinically in the treatment of lymphopathia venerea by a number of investigators.[36–38] All three have been found to be about equally effective in causing regression of buboes and subsidence of symptoms in early stages. The recurrence rate varies conversely with the duration of therapy. Since oxytetracycline is associated with less troublesome side reactions than the other two antibiotics, it would seem to be preferred. Oxytetracycline should be administered in divided doses of 1 to 2 Gm. daily and continued for about four weeks or at least until one week after symptoms have disappeared. Late lesions usually do not respond to antibiotics alone and must be corrected surgically with adjunctive antibiotic therapy.

Bartonellosis (Carrion's Disease). Bartonellosis, Oroya fever and verruga, caused by the polymorphous *Bartonella bacilliformis*, has been noted to respond favorably to chloramphenicol,[38] and, in vitro, *B. bacilliformis* has been found by Wigand[39] to be completely inhibited by oxytetracycline in only one one-hundredth the concentration required for either chlortetracycline or chloramphenicol.

It seems reasonable to assume that bartonellosis will manifest favorable clinical response to oxytetracycline therapy similar to that obtained with chloramphenicol.

Psittacosis (ornithosis). Psittacosis, an avian infection transmissible to humans and caused by a large elementary-body virus, has been observed to respond favorably to oxytetracycline in chick embryos and in mice; and preliminary clinical reports indicate that oxytetracycline is effective against psittacosis in humans.[41, 42]

Rickettsioses. Oxytetracycline therapy of rickettsial diseases is discussed in another section of this symposium.

TROPICAL TREPONEMATOSES*

Yaws (Pian, Frambesia). Yaws, a contagious, nonvenereal, tropical treponematosis, is caused by the *Treponema pertenue* entering the body usually through a break in the skin. After two to four weeks, a typical yellowish pink, granular, papillomatous primary lesion—the mother yaw (maman pian, bouba madre)—appears at the initial site of infection, usually on an exposed part of the body and most often on the leg below the knee. Three to eight weeks later, while the primary lesion is still manifest, constitutional symptoms occur and secondary eruptions, frambesiomas, appear. These are followed in untreated or in inadequately treated cases by a latent stage of variable duration and often after some months or years by destructive and deforming lesions that are characteristic of late or tertiary yaws.

The treatment of early yaws has been directed toward: (1) complete cure with destruction of all the treponemas in the body; or (2) checking contagion by merely eliminating the treponemas from and healing the early external lesions. It is apparent that the former, although initially more expensive, is ultimately inexpensive, since it promises assurance that late destructive lesions will be prevented, an ultimate

* This section was written by Elmer H. Loughlin in collaboration with Aurele A. Joseph and François Duvalier, Port-au-Prince, Haiti.

FIG. 1. Papillomatous frambesiomas treated with oxytetracycline intramuscular (0.75 Gm.). A (*Left*), before treatment. B (*Right*), 2 weeks later.

goal in antiyaws campaigns, that infectious cases will be reduced, that infectious relapses will not occur, and that new infections will be prevented. The latter, which is the sole aim of some mass eradication programs, disregards the possibility of infectious relapses occurring or late destructive lesions developing in inadequately treated cases. It should be recognized that frambesiomas of relapsed cases are just as infectious as those of previously untreated cases.

The authors have found oxytetracycline to be highly efficacious in the treatment of late as well as early yaws, whether administered orally,[43, 44] intravenously,[45] or intramuscularly.[46] Pronounced beneficent effects were achieved within a few days after beginning treatment with oxytetracycline and by 24 to 48 hours all of the treponemas had disappeared from the external lesions.[47] The bacterial contamination of heavily infected lesions was strikingly diminished within 24 hours. Primary lesions, uncomplicated by severe bacterial contamination and deep ulceration were usually dry on the second or third day of therapy and in some cases healing was complete by the fourth or fifth day. Primary lesions of exceptional size, heavily contaminated with bacteria or deeply ulcerated, were slower to heal. However, the topical application of crystalline oxytetracycline to such lesions effectively assisted drying and healing.

Secondary lesions, papillomatous, circinate, macular, papular, and condylomatous frambesiomas, responded quickly to oxytetracycline therapy with drying and healing

so marked at 24 and 48 hours that unless photographs had been made the extent of their regression could hardly have been appreciated. Within 24 hours, ulcerous as well as nonulcerous plantar lesions, which in many instances had been so painful that patients were unable to walk or stand without support or assistance, became considerably less painful. By 48 to 72 hours, they could walk on the affected parts of the soles, and by the fifth or sixth day they had completely useful lower extremities.

Late or tertiary yaws lesions responded favorably. Gummas disappeared; the progress of gangosa (rhinopharyngitis mutilans) was arrested; deforming osteoperiostitis, tenosynovitis, and dactylitis and indolent ulcerations regressed, especially when the latter were treated with systemically administered oxytetracycline later supplemented by topical applications of crystalline oxytetracycline.

Dosage of Oxytetracycline in Early Yaws. Crystalline oxytetracycline should be given orally in single doses for five consecutive days as follows: to children less than 5 years of age, 1 Gm. daily; to children between 5 and 10 years of age, 1.5 Gm. daily; to those more than 10 years old and to adults, 2 Gm. daily.

Oxytetracycline intramuscular should be administered for five consecutive days as follows: children less than 5 years of age, 150 mg. injected once daily; children between 5 and 10 years old, 200 mg. injected once daily; those more than 10 years old and adults, 250 mg. injected once daily.

Dosage of Oxytetracycline in Late Yaws. Although these dosages of oxytetra-

Fig. 2. Papillomatous frambesiomas treated with orally administered crystalline oxytetracycline. A (*Left*), before treatment. B (*Right*), 11 days later.

cycline are usually adequate to treat and arrest many cases of late yaws, indolent ulcerations, gummas, and deforming osteoperiostitis frequently require one or two additional courses of therapy. As already indicated we have found that topically applied crystalline oxytetracycline materially aids in drying, in maintaining ulcerations free of bacterial contamination, and in healing indolent ulcerations even when they have penetrated to the tendons and bone.

Since orally administered crystalline oxytetracycline and oxytetracycline intramuscular produce similar clinical effects in yaws, the latter might be considered preferable for treating small children among whom the incidence of early yaws is high; and because only small doses are injected, the cost of treatment with oxytetracycline should be reduced materially.

We have noted the following: the already mentioned dosages of oxytetracycline

FIG. 3. Ulcerous plantar lesion (frambesioma) treated with orally administered crystalline oxytetracycline and topically applied crystalline oxytetracycline. A (*Left*), before treatment. B (*Right*), 4 weeks later.

FIG. 4. Ulcerous plantar lesions (frambesiomas), osteitis, and periostitis treated with orally administered crystalline oxytetracycline and topically applied crystalline oxytetracycline. A (*Left*), before treatment. B (*Right*), 6 weeks later.

consistently produce drying and healing of frambesiomas at least as quickly as doses of 4.8 million units of repository penicillin, and these dosages provide more rapid and complete healing of ulcerous primary lesions, which if allowed to remain open for long periods, as happens frequently after repository penicillin therapy, would serve as foci for reinfection; healing of ulcerous and nonulcerous plantar lesions is more rapid with oxytetracycline than with repository penicillin therapy; the arrest and even healing of late yaws lesions with oxytetracycline is definitely more rapid and complete than that produced by repository penicillin in doses up to several times those already indicated.

Other investigators using oxytetracycline have also found this antibiotic to be an efficacious agent in the treatment of early yaws.[49–50]

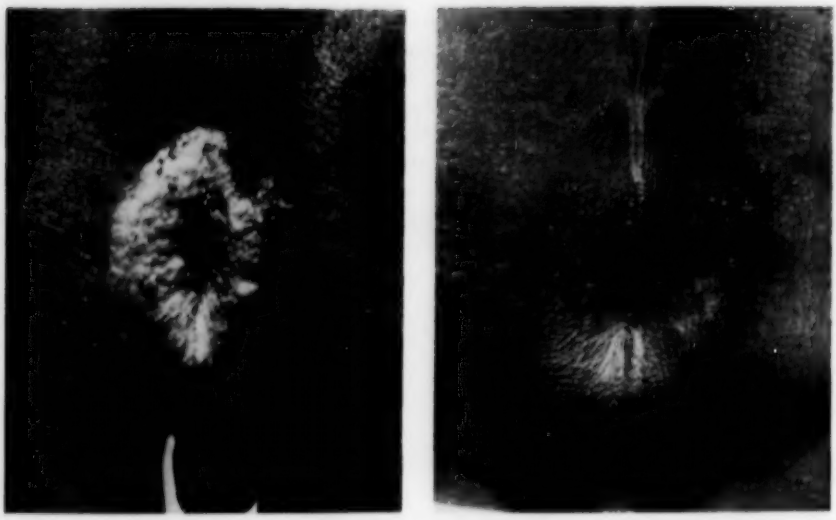

FIG. 5. Condylomatous frambesioma of perianal area treated with orally administered crystalline oxytetracycline. A (*Left*), before treatment. B (*Right*), 2 weeks later, site of lesions marked by residual slight thickening and dyschromia of skin.

We cannot agree with the assumption of one investigator that the infrequency of Herxheimer reactions in oxytetracycline-treated cases and the generally higher frequency of such reactions, although not an invariable occurrence, in repository penicillin-treated cases indicates a bacteriostatic rather than a bactericidal effect for oxytetracycline as contrasted to penicillin.[51] Although the etiology of Herxheimer reactions is usually thought to result from the sudden destruction of large numbers of treponemas and the liberation of their split products into the tissues, existing evidence does not strongly support this view.[52] We have encountered Herxheimer reactions in yaws after small (300,000 units) as well as after large (1.2 to 1.8 million units) doses of repository penicillin with no predictable regularity. The relapse rates in cases treated with 300,000 to 600,000 unit doses of repository penicillin were at least several times higher than those treated with 1.2 to 1.8 million unit doses,[53] proving the need for the higher dosage.

Pinta (Carate). Pinta, a tropical treponematosis possibly related to yaws, is caused by the *Treponema carateum*. Because the initial lesion is not conspicuously manifest, the patient seldom notices or later recalls its site of occurrence. The best descriptions of the primary lesions of pinta have been derived from watching experimentally inoculated volunteers. After two or three weeks, a papule evolves at the site of inoculation and enlarges peripherally developing into an erythematous scaly macule that soon may become dyschromic. Two to six months later, disseminated secondary scaly papular and macular lesions appear in different regions. The initial

lesion, which generally persists, cannot be distinguished from the secondary lesions. The latter, unlike the late lesions are not usually symmetrical. The dyschromias may be quite marked in different lesions and cases with gradations from achromia through slate blue or black hyperchromia are encountered. Subsequently, after varying periods with no definite demarcation between stages, the late or tertiary lesions begin to make their appearance. These lesions, which are dyschromic, become achromic in patches that develop a remarkable symmetry when they occur on the extremities, breasts, buttocks, and face. The texture of the involved skin also changes so that gradations from parchment-like atrophy to extremely thick elephantine hyperkeratoses of the feet, ankles, hands and wrists, knees, and elbows are seen.

We have observed patients who were treated with repository penicillin with dosages up to several million units, and quite contrary to published reports many of the lesions continued to progress and treponemas were found in skin fluid;[47] the incidence being generally converse to the amount of penicillin that had been given. On the other hand, with dosages of oxytetracycline similar to those that we used in yaws we obtained clearing of the treponemas from skin fluid equal to that produced by 4.8 million units of repository penicillin. Late lesions of pinta generally do not respond satisfactorily to antibiotic therapy. We believe that there are other factors that are responsible for their evolution and resistance to antitreponemal therapy.

FIG. 6. Deep indolent ulceration (late yaws) treated with orally administered crystalline oxytetracycline and topically applied crystalline oxytetracycline. A (*Left*), before treatment. B (*Right*), 3 months later after three courses of oral oxytetracycline therapy. Albinismus universalis with pigmented lentigines (not due to yaws).

Results of investigations that we have conducted to determine the role of these factors appear to substantiate these beliefs.[55]

Bejel. Bejel is a contagious tropical treponematosis that is geographically almost entirely limited to the Euphrates Valley and its Bedouin inhabitants. Although the lesions of the early and late stages of bejel resemble those of yaws more than syphilis, its exact relationship to these treponematoses and the role of venereal transmission

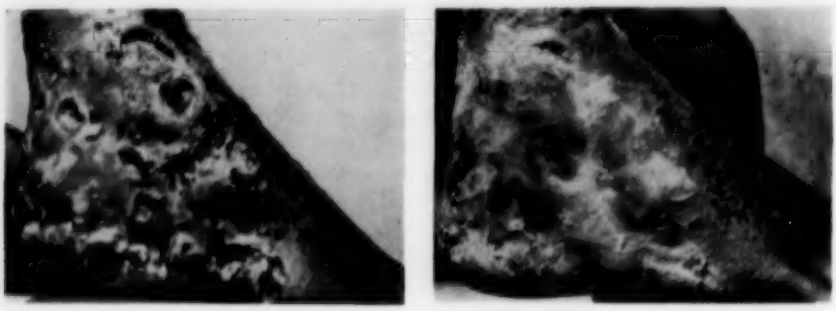

FIG. 7. Indolent ulcerations, periostitis (late yaws) treated with orally administered crystalline oxytetracycline and topically applied crystalline oxytetracycline. A (*Left*), before treatment. B (*Right*), 2 months later, full use of foot and ankle.

are not settled. The causative treponema possess the morphologic features and motility of *Treponema pallidum*. Like the other treponematoses, serologic reactions (Wassermann, Kahn) are usually positive. However, unlike syphilis but like yaws and pinta, congenital bejel is not seen.[56–57]

We are not aware of any reports concerning the use of oxytetracycline in the treatment of bejel but, because favorable results have been obtained with the use of repository penicillin, it is highly probable that similarly favorable results might be obtained with the use of oxytetracycline.

MISCELLANEOUS SPIROCHETAL DISEASES

Rat Bite Fever. Rat Bite Fever, caused by *Spirillum minus*, has been found to respond favorably to therapy with oxytetracycline.[58]

Relapsing Fever. Relapsing Fever (tick borne), caused by *Borrelia recurrentis*, has been noted to respond favorably to therapy with oxytetracycline;[59] and in vivo, oxytetracycline has been observed to sterilize the blood of rats experimentally infected with *B. recurrentis*.[60]

Weil's Disease (Leptospirosis). Weil's disease is caused by *Leptospira icterohaemorrhagiae*. Although broad-spectrum antibiotic therapy of experimental infections has indicated possible clinical effectiveness, it is still evident from scattered clinical reports that more investigations on the treatment of human cases with these antimicrobial agents are necessary before their status in this disease can be defined.

TROPICAL ULCER*

Tropical Ulcer (Phagedenic Ulcer). Tropical ulcer is a peripherally and gravitationally spreading ulceration of indeterminate etiology occurring usually on a lower extremity near the ankle or on the foot. Malnutrition, trauma from insect bites, abrasions, blisters caused by burns and friction, and infection, common skin aerobic bacteria, anaerobes, fusiform bacilli and spirochetes, dirt, and local sympathetic nervous and vascular disorders are considered as factors in its pathogenesis. Beginning as a papule or as an erythematous area at or around the site of trauma, ulceration develops with a surrounding satellite arrangement of secondary vesicles. After varying periods from a few weeks to many months, a typical chronic, extensive phagedenic ulcer evolves with usually a granular, sloughing base that is weeping sanguineous or seropurulent fluid and an elevated, undermined margin, or less frequently it has a smooth and relatively dry meaty base with a sloping fibrous and keratinized margin. As the ulcer extends peripherally, it generally penetrates deeper and exposes tendons and even periosteum. Surrounding the ulcer there is usually a variable inflammatory reaction with edema, the skin having an eczematoid and cutis rhomboidea appearance with thickening, dyschromia, and frequently marked local sweating.

Local as well as systemic therapy is indicated. The latter should include a suitable diet high in protein with vitamin supplements, especially A. The use of systemic antimicrobial therapy is optional. In Haiti, where yaws is endemic, we gave oxytetracycline according to the dosages used in treating yaws. Since we had obtained such favorable results in ulcerous lesions of late yaws with topically applied crystalline oxytetracycline, we supplemented systemic therapy with daily topical applications of crystalline oxytetracycline to the base and margins of ulcers. The response of early lesions to combined oxytetracycline therapy was excellent; healing was complete within two or three weeks. However, longstanding chronic ulcers were notably slower in their response with 18 of 35 cases closing completely within six to eight weeks. Very extensive deep ulcers failed to close with oxytetracycline or any other therapy.[61] Nevertheless, most of these cases were so tremendously improved that they could return home and resume gainful work. The response of tropical ulcers to topically applied crystalline oxytetracycline was so favorable that we venture the opinion that, when crystalline oxytetracycline is continually in contact with tropical ulcers, it exhibits not only an antimicrobial effect, as manifested by the disappearance of fusiform bacilli and spirochetes within 24 hours and sterilization of ulcers within 24 to 48 hours, but a growth stimulating effect on the tissues as well. Oxytetracycline (30 mg./Gm.) ointment applied twice daily to six tropical ulcers of less than four weeks' duration produced complete healing in all.[62]

* This section was written by Elmer H. Loughlin in collaboration with Aurele A. Joseph and Francois Duvalier, Port-au-Prince, Haiti.

IN CONCLUSION

The range of effectiveness of oxytetracycline in so many etiologically distinct tropical diseases is so remarkably broad as to be almost incredible. We are prompted at this point to express our current thoughts regarding oxytetracycline in tropical medicine in the words of Kipling, "These are the magic. These are the vision. The rest is only poetry."

BIBLIOGRAPHY

1. Martin, G. A.; Garfinkel, B. T.; Brooke, M. M.; Weinstein, P. P., and Frye, W. W.: Comparative efficacy of amebacides and antibiotics in acute amebic dysentery; used alone and in combination in five hundred thirty-eight cases, J.A.M.A. *151*:1055–1059, 1953.
2. Killough, J. H., and Magill, G. B.: Terramycin in epidemic typhus, amebic dysentery, and typhoid, J.A.M.A. *147*:1737–1740, 1951.
3. Loughlin, E. H.; Mullin, W. G., and Joseph, A. A.: Unpublished observations in 16 cases of acute amebic dysentery treated with Terramycin.
4. Elsdon-Dew, R.: Antibiotics in acute ulcerative amebic colitis. In: Antibiotics Annual 1954–1955, New York, Medical Encyclopedia, Inc., 1955, pp. 869–875.
5. Most, H., and Van Assendelft, F.: Treatment of amoebiasis with terramycin, Ann. New York Acad. Sc. *55*:1114–1117, 1952.
6. Tobie, J. E.; Most, H.; Reardon, L. V., and Bozicevich, J.: Laboratory results on the efficacy of terramycin, aureomycin and bacitracin in the treatment of asymptomatic amebiases, Am. J. Trop. Med. *31*:414–419, 1951.
7. Loughlin, E. H.; Mullin, W. G., and Joseph, A. A.: Unpublished data.
8. Most, H., and Van Assendelft, F.: Laboratory and clinical observations on the effect of terramycin in the treatment of amebiasis, Am. J. Trop. Med. *31*:284–285, 1951.
9. Ruiz-Sanchez, F.; Riebelino, R., and Arreola, C.: El tratamiento de la disenteria amibiana con tetramicina. Medicina, México *30*:365–369, 1950.
10. Mériel, P.; Darnaud, C.; Denard, Y.; Clavière, P.; Commanay, L., and Sardou, R.: Efficacité de la terramycine dans 15 cas de dysenteries amibiennes rebelles, Arch. mal. app. digest. *42*:113–116, 1953.
11. McHardy, G., and Frye, W. W.: Antibiotics in management of amebiasis, J.A.M.A. *154*:646–651, 1954.
12. Charmot, G., and Le Henand, F.: Dix observations d'ambiase hépatique traitées par la terramycine, Bull. méd. de L'Afrique-Occidentale Française *9*:259–264, 1952.
13. Neghme, A.; Miranda, M.; Aodin, M., and Sanz, R.: Contribución a la quimioterapia del *Balantidium coli*, Bol. de Informaciones Parasitarias Chilenas, *6*:7–8, 1951.
14. Weinstein, P. P.; Garfinkel, B. T., and Miller, M. M.: Treatment of a case of balantidial dysentery with terramycin, Am. J. Trop. Med. *1*:980–981, 1952.
15. Hoekenga, M. T.: Terramycin treatment of balantidiasis in Honduras, Am. J. Trop. Med. 2:271–272, 1953.
16. Loughlin, E. H., and Mullin, W. G.: Unpublished data.
17. Coatney, G. R., and Greenberg, J.: The use of antibiotics in the treatment of malaria, Ann. New York Acad. Sc. *55*:1075–1081, 1952.
18. Ruiz-Sanchez, F.; Lidoff, I.; Paredes, M., and Riebelino, R.: Dos casos de paludismo tratados con terramicina Medicina, México *31*:223–224, 1951.
19. Ruiz-Sanchez, F.; Casillas, J.; Paredes, E. M.; Velazquez, J., and Riebelino, R.: Terramycin in the treatment of malaria, Antib. & Chemo. 2:51–57, 1952.
20. Loughlin, E. H., and Joseph, A. A.: Unpublished observations.
21. Wells, H. S.: Studies of the effect of antibiotics on infections with the mouse pinworm, *Aspiculuris tetraptera*. I. The action of terramycin hydrochloride, J. Infect. Dis. *89*:190–192, 1951.
22. Loughlin, E. H.; Mullin, W. G.; Rappaport, I., and Joseph, A. A.: Some effects of oxytetracycline on certain intestinal helminths. (In press.)

23. Loughlin, E. H.; Rappaport, I.; Mullin, W. G.; Wells, H. S.; Joseph, A. A., and Shookhoff, H. B.: The treatment of enterobiasis with terramycin base, Antib. & Chemo. *1*:588–593, 1951.
24. Loughlin, E. H., and Mullin, W. G.: The treatment of enterobiasis with crystalline oxytetracycline. Antib. Med. *1*:147, 1955.
25. Hardy, A. V.; Mason, R. P., and Martin, G. A.: The antibiotics in acute bacillary dysentery, Ann. New York Acad. Sc. 55:1070–1074, 1952.
26. Meyer, K. F.; Quan, S. F.; McCrumb, F. R., and Larson, A.: Effective treatment of plague, Ann. New York Acad. Sc. 55:1228–1274, 1952.
27. McCrumb, F. R., Jr.; Mercier, S.; Robic, J.; Bouillat, M.; Smadel, J. E.; Woodward, T. E., and Goodner, K.: Chloramphenicol and terramycin in the treatment of pneumonic plague, Am. J. Med. *14*:284–293, 1953.
28. Sokhey, S. S.; Wagle, P. M., and Habbu, M. K.: Treatment of bubonic plague with sulfonamides and antibiotics, Bull. World Health Organ. *9*:637–643, 1953.
29. Girard, G.: Le traitement de la peste par les antibiotiques fungiques. A propos de 25 cas traités à Madagascar, Rev. Coloniale de méd. et chir. *24*:174–180, 1952.
30. Quan, S. F.; Chen, T. H., and Meyer, K. F.: Protective action of antibiotics against the toxin of *Pasteurella pestis* in mice, Proc. Soc. Exper. Biol. & Med. *75*:548–549, 1950.
31. Felsenfeld, O., and Soman, D. W.: Treatment of cholera with antibiotics, Ann. New York Acad. Sc. 55:1059–1062, 1952.
32. Das, A.; Ghosal, S.; Mondal, A., and Gupta, S. K.: Terramycin in cholera, J. Indian M. A. *22*: 268–271, 1953.
33. Das, A.; Ghosal, S., and Gupta, S. K.: Intravenous terramycin in cholera, J. Indian M. A. *22*:272–273, 1953.
34. Whitaker, J. C.; Wright, L. T.; Brinfield, M. S.; Wilkinson, R. S., and Marmell, M.: Oral terramycin in granuloma inguinale, Antib. & Chemo. *1*:208–210, 1951.
35. Wright, L. T.; Prigot, A.; DiLorenzo, J. C.; Whitaker, J. C., and Marmell, M.: Oral terramycin in the rapid treatment of gonorrhea and other veneral diseases, Am. J. Syph., Gonor. & Ven. Dis. *35*: 482, 1951.
36. Greenblatt, R. B.: Antibiotics in treatment of lymphogranuloma venereum and granuloma inguinale, Ann. New York Acad. Sc. 55:1082–1089, 1952.
37. Wright, L. T.; Whitaker, J. C.; Wilkinson, R. S., and Brinfield, M. S.: The treatment of lymphogranuloma venereum with terramycin; report of twenty successfully treated cases, Antib. & Chemo. *1*:193–197, 1951.
38. Niedelman, M. L.; Pierce, H. E., Jr.; Hoffstein, L. D., and Matteucci, W. V.: Terramycin in the treatment of chancroid, lymphogranuloma venereum and granuloma inguinale, Am. J. Syph., Gonor. & Ven. Dis. *35*:482–487, 1951.
39. Payne, E. H., and Urteaga, O.: Carrion's disease treated with chloromycetin, Antib. & Chemo. *1*: 92–99, 1951.
40. Wigand, R.: Neue Untersuchungen über *Bartonella bacilliformis*. 2. Mitteilung: Verhalten gegenüber Sulfonamiden und Antibiotica *in vitro*, Zeschr. f. Tropenmed. u. Parasitol. *3*:453–460, 1952.
41. Pollard, M.; Bussell, R. H.; Benedict, A. A., and Wilson, R.: The response of three human infections of psittacosis to antibiotic therapy, Antib. & Chemo. *4*:138–140, 1954.
42. Hurst, E. W.; Peters, J. M., and Melvin, P.: The therapy of experimental psittacosis and lymphogranuloma venereum (inguinale). I. The comparative efficacy of penicillin, chloramphenicol, aureomycin, and terramycin, Brit. J. Pharmacol. *5*:611–624, 1950.
43. Loughlin, E. H., and Joseph, A. A.: Terramycin in the treatment of yaws, Antib. & Chemo. *1*:76–87, 1951.
44. Loughlin, E. H.; Joseph, A. A., and Duvalier, F.: Le traitement du pian par la terramycine pure, Gaz. Méd. France *59*:1075–1078, 1952.
45. Loughlin, E. H.; Joseph, A. A., and Duvalier, F.: Unpublished data.
46. Loughlin, E. H., Joseph, A. A., and Duvalier, F.: Oxytetracycline intramuscular in the treatment of yaws (pian), Antib. & Chemo. *4*:155–164, 1954.
47. Loughlin, E. H.; Joseph, A. A., and Schaffer, K.: Phase contrast microscopy for demonstration of *Treponema pertenue* in yaws lesions, Am. J. Trop. Med. *31*:26, 1951.

48. Guimarães, F. Nery, and Travassos, J.: Ação da terramicina na bouba (framboesia, pian, yaws); nota preliminar, Hospital, Rio de Janeiro, *38*:295–299, 1950.
49. Ampofo, O., and Findlay, G. M.: Terramycin in treatment of yaws and tropical ulcer, Tr. Roy. Soc. Trop. Med. Hyg. *45*:261–263, 1951.
50. Hill, K. R.: Tratamiento del pian con antibióticos distintos de la penicilina, Bol. Ofic. san. panam. *35*:147–162, 1953.
51. Rein, C. R.: Treatment of yaws with antibiotics, Ann. New York Acad. Sc. *55*:1176–1185, 1952.
52. Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Co., 1952.
53. Loughlin, E. H., Joseph, A. A., and Duvalier, F.: The antibiotics in the treatment of yaws. Read in part at the Annual Meeting of the American Society of Tropical Medicine, Savannah, November 9, 1950. In press.
54. Loughlin, E. H., Joseph, A. A., and Duvalier, F.: Unpublished observations.
55. Hudson, E. H.: Bejel: The endemic syphilis of the Euphrates Arab, Tr. Roy. Soc. Trop. Med. & Hyg. *31*:9–33, 1937.
56. Hamelmann, C. M.: Syphilis among Arabs in the Near East; bejel and loath in Iraq and Syria; firjal and latta in Palestine; laghout in Lebanon; abou-laghif and jifár in Trans-Jordan, Arch. Dermat. & Syph. *38*:837–855, 1938.
57. Hudson, E. H., and Crosley, S. S.: The influence of bejel on the second generation, Brit. J. Dermat. *48*:288–299, 1936.
58. Sen, S.; Basu, B. C., and Banerjee, D.: Streptomycin and terramycin in the treatment of rat-bite fever due to *Spirillum minus*, Indian Med. Gaz. *89*:3–9, 1954.
59. Gefel, A., and Rubenow, R.: Terramycin in the treatment of relapsing fever, Harefuah *44*:263–265, 1953.
60. Hobby, G. L.; Dougherty, N.; Lenert, T. F.; Hudders, E., and Kiselyk, M.: Antimicrobial action of terramycin *in vitro* and *in vivo*, Proc. Soc. Exper. Biol. and Med. *73*:503–511, 1950.
61. Loughlin, E. H.; Price, C. W., and Joseph, A. A.: Streptomycin—bacitracin—polymyxin combinations; the application of multiple antibiotic combinations in prophylaxis of skin infections with common bacteria and the treatment of chronic (tropical) ulcers. *In:* Antibiotics Annual, 1953-1954, New York, Medical Encyclopedia, Inc., 1953, pp. 291–293.
62. Ampofo, O., and Findlay, G. M.: Treatment of tropical ulcer with terramycin ointment. Tr. Roy. Soc. Trop. Med. and Hyg. *46*:650–652, 1952.

The Use of Oxytetracycline in the Treatment of Certain Tropical Diseases

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There have been many new developments in the treatment, prevention, and control of some of the tropical diseases during and since the close of the second world war. There still remains a number of diseases for which there is no effective therapeutic agent. The discovery of the antibiotics led to a wide trial of these substances in the treatment of almost all of the tropical diseases. As a result of this interest in the antibiotics, there has been a mass of information accumulated regarding the results of therapeutic trials. The antibiotics have been of great value in the treatment of some of these diseases and of no value in others. Certain of the antibiotics have made possible the control of specific diseases that have been a major factor in retarding progress in certain tropical countries. Antibiotics have made possible international health campaigns for mass treatment and control of certain infectious diseases. It is impossible to describe all of the benefits that have accumulated as a result of antibiotic therapy in tropical diseases, but there have been many.

The diseases of man caused by animal parasites have been and continue to be major causes of disability and death in many parts of the world. Some of the parasitic diseases, such as schistosomiasis, are still major therapeutic problems. The antibiotics have been much less effective in these animal parasitic diseases as a group than in the bacterial and spirochetal diseases. The broad-spectrum antibiotics have been more effective against certain protozoan diseases than against the helminths. With the discovery and development of new antibiotics it is hoped that more effective treatment of the diseases caused by animal parasites will be found.

AMEBIASIS

Since the discovery of oxytetracycline,* its value in the treatment of amebiasis has been studied in many parts of the world. This antibiotic has been evaluated in all forms of amebiasis from severe dysentery to the symptomless carrier. In a preliminary report in 1950 Most and Van Assendelft[1] treated 22 patients with 1 to 2 Gm. of oxytetracycline daily by mouth for 10 days. One parasitic relapse occurred in this group 11 days after treatment was completed. The remaining 21 patients were negative and of this group 18 had been followed for three weeks or less and 3 for more than two months. Most and Van Assendelft[2] a year later reported the results of further follow-up observations on the original patients, as well as the results of treatment with oxytetracycline of additional cases of amebiasis. These studies indicated that broad-spectrum antibiotics were highly effective in eradicating *Enda-*

* The trade name of Chas. Pfizer & Co. for oxytetracycline is Terramycin.

moeba histolytica from the intestinal tract for periods up to 6 months or more, and that the daily dose of oxytetracycline in the adult should be at least 2.0 Gm. They noted that oxytetracycline was not effective against the intestinal helminths and flagellates in the intestinal tract of this group of patients.

Tobie, Most, Reardon, and Bozicevich[3] reported the results of mass therapy, using oxytetracycline, in a state mental hospital. Careful laboratory studies had shown that 49 per cent of the inhabitants were infected with *E. histolytica*. The individuals harboring *E. histolytica* in this study were asymptomatic. Two hundred and twenty-two inhabitants of the infirmary were treated with oxytetracycline. The dosage schedule was 2 Gm. daily for 10 days for patients weighing more than 75 lb., and 1 Gm. daily for those weighing less than 75 lb. With this schedule of therapy, examinations two weeks and two and one-half months after completion of therapy were negative for *E. histolytica* on all patients. At the end of six months, the oxytetracycline treated group was still negative. In this mass therapeutic trial oxytetracycline was 100 per cent effective. These workers also noted that there was some effect on other nonpathogenic intestinal amebae in this group of individuals, but a careful evaluation of the nonpathogenic amebae and other animal parasites was not made.

During 1951 Killough and Magill[4] reported results of treatment in 7 cases of acute amebic dysentery with oxytetracycline. All of the patients had bloody diarrhea with mucus, and stool examinations revealed numerous motile trophozoites of *E. histolytica*. Two of these patients had previously been treated with chlortetracycline.* The total amount of oxytetracycline given in a 14 day period was 66 Gm. The initial dose was 60 mg./Kg. of body weight, followed by 150 mg./Kg. per day for the first three days, after which the dose was reduced to 75 mg./Kg. per day for the remainder of the 14 days. Stools and proctoscopic specimens became negative for *E. histolytica* after two days in 4 patients, and after four to eight days in the rest. In 1 patient a liver abscess developed during oxytetracycline therapy. Five of the patients were followed for three to five months. In 2 of these 5 patients there was a reappearance of the parasite in the stools.

Early in 1952 Elsdon-Dew, Armstrong, and Wilmot[5] used oxytetracycline in the treatment of patients having diarrhea with blood and mucus in the stools, with ulceration of the mucosa seen on sigmoidoscopy and with actively motile *E. histolytica* in stools or ulcer scrapings. Any cases showing liver manifestations were excluded. In a series of 49 patients, 1 Gm. of oxytetracycline was given daily for 15 days. Daily sigmoidoscopy was done on each patient. In 8 patients ulcers were healed by the fourth day and in 32 by the seventh day. The amebae had disappeared from the lesions by the fourth day in 77.6 per cent and by the seventh day in 89.7 per cent of the patients. Two patients started on treatment with oxytetracycline at the same time as the group of 49 and receiving the same dosage developed hepatitis, which progressed in spite of treatment. This necessitated the use of emetine on the sixteenth day in one case and chloroquine on the sixth day in the second. Both cases

* The trade name of the Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline is Aureomycin.

were "successes" from the intestinal standpoint before the emetine or chloroquine were used to treat the liver involvement. These results showed that oxytetracycline produced an immediately apparent cure in a very high proportion of cases of acute ulcerative amebic dysentery. These workers discuss briefly the possible mode of action of oxytetracycline considering whether it is an effect on the intestinal bacteria or on the amebae. At the present time we know that oxytetracycline has a direct effect on the associated bacterial flora of the intestinal tract, but there is also increasing evidence showing that there is a direct amebacidal effect.

Frye, Brooke, and Weinstein[6] gave a preliminary report on the use of certain antibiotics in the treatment of acute amebic dysentery in the United Nations prisoner-of-war camp in Korea during 1951. Oxytetracycline was found to be the most effective of three antibiotics used. All patients were followed for a period of six weeks after completion of therapy. Martin et al[7] gave a complete report of the prisoner-of-war camp study showing the comparative efficacy of antibiotics and other amebacides in the treatment of acute amebic dysentery. The antibiotics and other amebacides were used alone and in combination in the treatment and six weeks' follow-up of 538 acutely ill patients. The criteria for acceptance of a diagnosis of acute amebic dysentery in this study were the presence of diarrheal disease with mucosanguinous exudate in the stools, visualized enteric lesions, and the presence of trophozoites of *E. histolytica*. No asymptomatic patients with only cysts of *E. histolytica* were considered in this study. Oxytetracycline proved to be the most effective of the antibiotics studied. A total of 104 patients were treated with oxytetracycline in varying dosages and all responded clinically. Six of the 104 patients relapsed, 3 early in the follow-up period and 3 later. One of these 6 had clinical amebic hepatitis. The remaining 98 were well and free of evidence of recurrent infection at the end of six weeks. There were surprisingly few gastrointestinal side reactions to oxytetracycline among this group of patients.

The question of extraintestinal amebiasis must be emphasized at this point in the discussion of oxytetracycline in the treatment of intestinal amebiasis. Martin et al[7] described 1 patient who was treated successfully with oxytetracycline as far as the intestinal disease was concerned but who developed septic fever, leukocytosis, and hepatic enlargement and tenderness. These symptoms subsided following therapy with chloroquine. Killough and Magill[4] report a case in which a liver abscess developed during treatment with oxytetracycline. The advisability of combining this antibiotic with chloroquine or emetine in patients showing any signs of liver involvement must be considered carefully. From the information now available it is clear that oxytetracycline and other antibiotics are indicated in the treatment of amebic abscess of the liver only if heavy secondary bacterial infection has occurred. There are no reported cases of skin amebiasis treated with oxytetracycline alone.

Recently Sappenfield et al[8] reported on their experiences with oxytetracycline in the treatment of a large group of individuals involved in a water-borne outbreak of amebiasis. This outbreak was discovered during the spring of 1953. A contaminated water supply was considered to be the most probable source of infection with *E. histolytica*. The epidemic was confined to the employees of a woodworking plant. Of a random sample of employees submitting a single stool specimen for examination,

51 per cent were found infected with *E. histolytica*. Stool specimens were then obtained from all employees and examined for *E. histolytica* and other intestinal parasites. The examinations were repeated until a diagnosis of amebiasis was made or until 4 negative specimens had been submitted.

Oxytetracycline was used to treat 405 of the individuals found infected. One Gm. of oxytetracycline was given twice daily for a period of 10 days. A treatment schedule was arranged so that one half of the daily medication was taken in the morning in a treatment center set up in the plant. The other half of the daily dose was given to the patient to be taken just before leaving the plant at the end of the day's work. During the entire 10 day period of therapy, there was daily contact between each employee and the medical personnel supervising the treatment program. A record of complaints was kept on each patient. During the first month after completion of therapy, frequent contact with each employee was necessary to obtain follow-up stool specimens.

The most common complaints recorded during the 10 day treatment period with oxytetracycline were loose stools, moderate abdominal cramping, and varying degrees of nausea. These complaints appeared more frequently after the fourth day of therapy and usually lasted from 48 to 72 hours.

Anal itching was the most frequent complaint occurring after oxytetracycline therapy was completed. This usually cleared if the area was kept clean and a bland ointment applied to protect against moisture. None of the individuals treated missed work because of any reaction from the oxytetracycline.

Oxytetracycline and fumagillin were used in alternate patients found infected with *E. histolytica*. Oxytetracycline was chosen for this study in order to confirm its effectiveness in a large number of asymptomatic cases in which a long follow-up period was possible. Of the 405 treated with oxytetracycline, records and follow-up were complete on 358 individuals. After one course of therapy with oxytetracycline, 338, or 94.4 per cent, of the individuals treated had four negative stool examinations over a four month period.

This study showed that oxytetracycline was effective in eliminating *E. histolytica* from the intestinal tract of a large group of asymptomatic cases of amebiasis. This is the most common type of infection with *E. histolytica* seen by physicians in the United States. However, the danger of extraintestinal amebiasis is always present in individuals harboring *E. histolytica*. It has now been more than one year since this treatment program was completed, and there have been no reports of liver abscess or other extraintestinal amebiasis in the 405 patients treated with oxytetracycline for a period of 10 days.

The results of this study supply additional evidence that oxytetracycline is an effective, safe, relatively nontoxic amebacide that will aid the physician treating intestinal amebiasis. It was also demonstrated, in a large group of ambulatory patients treated with oxytetracycline, that the reactions to the antibiotic were usually mild and disappeared after completion of therapy.

The studies that have been reported on the use of oxytetracycline in the treatment of amebiasis show that this antibiotic is effective in eliminating the parasite from the intestinal tract. Oxytetracycline in the treatment of extraintestinal amebiasis

has been much less effective, and liver abscess has developed in patients while under treatment. The use of a combination of oxytetracycline and chloroquine or emetine has proved effective in the treatment of patients with amebic abscess of the liver.

YAWS

The first report of the use of oxytetracycline in the treatment of yaws was published by Loughlin and Joseph[9] in 1951, who treated a series of 150 patients in both early and late stages. An initial group of patients were treated with an arbitrary dose of oxytetracycline, 7 Gm. orally over a three day period; a single dose of 3 Gm. on the first day and 2 Gm. on the second and third days. This regimen of therapy was found to be satisfactory in that rapid clearing of the primary and secondary lesions occurred and rapid elimination of the treponemas from these lesions was obtained. At the end of a two months' period of observation, 2 of the patients were found to have infectious cutaneous lesions and were considered to be instances of relapse. Following this, the remaining 85 in the test group were treated with five daily doses of 2 Gm. each for a total of 10 Gm.

With either the three and five day schedules using oxytetracycline, the exudates of infectious lesions, which immediately prior to treatment had been swarming with treponemas, were observed to contain considerably fewer after a few hours. In more than 80 per cent of the cases the treponemas disappeared from the lesions at the end of 24 hours, while at 48 hours none could be found in any case. Primary lesions, uncomplicated by severe bacterial infections or deep ulceration, became dry on the second or third day of therapy and in some cases healing was practically complete by the fourth day.

Secondary lesions responded amazingly rapidly to orally administered oxytetracycline. Healing and drying were marked at the end of 48 hours. The crusts of the lesions usually became detached by the fifth or sixth day. The lichenoid, papular, and circinate lesions cleared even more rapidly so that by the fifth day they had practically disappeared. Wet ulcerated plantar lesions were dryer and cleaner at 24 hours, and by the eleventh day, unless extremely large and secondarily infected, they were completely healed. These wet plantar lesions were made painless within 24 to 48 hours and individuals, who could barely stand before treatment with oxytetracycline was started, could walk unaided on the third day of treatment.

These authors concluded that the response obtained in primary and secondary yaws with oxytetracycline therapy was far greater and more rapid than with other forms of therapy. The effects of oxytetracycline in tertiary yaws was no less startling. The use of topical therapy in addition to systemic therapy accomplished the rehabilitation of a number of patients who would previously have been considered hopeless cripples. In the authors' opinion, procaine penicillin, while satisfactory in early yaws, falls short of expectations in the treatment of late yaws. With oxytetracycline administered systemically and topically, arrest or in many cases marked improvement of these disfiguring and crippling lesions of late yaws can be obtained, something rarely accomplished by procaine penicillin.

More recently Loughlin, Joseph, and Duvalier[10] reported on the use of oxytetracy-

cline intramuscular in the treatment of yaws. In this study 120 patients, all West Indians, were selected for study solely on the basis of obtaining representative smears of early and late yaws. Eighty-four patients were male, their ages ranging from 5 months to 60 years, and 36 females whose ages ranged from 7 months to 69 years. One hundred and eight patients had early yaws. Twelve patients had late yaws lesions, such as gumma, gangosa (rhinopharyngitis mutilans), osteoperiostitis, and dactylitis or indolent ulcerations.

After testing several treatment regimens to determine the dose that would produce healing comparable to that obtained with the oral administration of oxytetracycline, adults and children more than 10 years of age were given 250 mg. intramuscularly once daily for five days, and children less than 5 years of age were given 150 mg. daily for five days. The intramuscular injections were given in the upper outer quadrant of the buttocks.

The authors state that intramuscular oxytetracycline, in the doses used in this study did not cause local irritation, residual swelling, or soreness. There were no instances of allergic or Herxheimer reactions in this group of patients with the oral or intramuscular use of oxytetracycline. Herxheimer reactions were recorded by the same investigators in cases of yaws treated with penicillin. Although both oral and intramuscular injections of oxytetracycline produce similar effects in yaws, the authors point out the following advantages of the intramuscular method of therapy: the treatment of yaws in small children can be made easier by daily intramuscular injections, the small doses of oxytetracycline given intramuscularly do not cause gastrointestinal disturbances and are well tolerated locally at the site of injection, and the small intramuscular doses required to obtain a therapeutic effect in yaws should reduce the cost of treatment of this infection with oxytetracycline.

Four of the patients treated presented themselves again after three or four months with new or recently healed primary lesions and frambesiomas. These patients had returned to their villages where yaws was still prevalent and on the basis of all factors involved these patients were considered as instances of reinfection. Two other patients, who returned with frambesiomas, did not have any evidence of a new primary lesion and were considered as relapsed cases.

With regard to the destructive and deforming lesions both with the oral and intramuscular administration of oxytetracycline, the authors state that the spectacular healing following therapy clearly demonstrated that this antibiotic is the most effective therapy for late yaws. They found that transforming these patients from invalids with advanced destructive lesions to productive members of the community had a remarkable effect on the morale of the entire community.

The serologic responses of these patients treated with oxytetracycline as well as with procaine penicillin are still being observed. It was noted that the serologic responses, following therapy with the antibiotics, were extremely variable, although in many instances two years had elapsed since completion of therapy. These investigators raise the question of the feasibility of trying to evaluate yaws therapy entirely from a serologic standpoint.

From the reports to date the evidence indicates that oxytetracycline is the most effective antibiotic now available for the treatment of the late manifestations of

yaws. Although this antibiotic is effective in all stages, the most spectacular results were obtained in the healing of the destructive and deforming lesions, which have been resistant to procaine penicillin therapy in mass control studies.

BEJEL, PINTA, AND OTHER SPIROCHETAL DISEASES

Although yaws is one of this group of diseases, it has been discussed separately because oxytetracycline has been studied and used more extensively in its treatment than in other related diseases.

Bejel, like yaws, is usually transmitted nonvenereally in childhood. The distribution of these and related diseases are of interest in relation to therapy and mass control. Bejel is common among seminomadic Bedouins of Arabia. In Europe yaws and pinta are absent, whereas in Africa yaws predominates and in Mexico pinta is prevalent. Syphilis has a world-wide distribution.

Hudson,[11] in his review of the treponematoses, presents the view that treponematosis is a universally distributed disease caused by *Treponema pallidum*, the only species of this genus. There are many facts relating to the bacteriology and serology of the treponemal diseases (syphilis, yaws, bejel, and pinta) which support this view. All agree that this group of diseases has a treponemal etiology. The organisms are similar morphologically and cannot be cultured satisfactorily. Hudson believes that the diseases caused by the treponemas are the same but have changed in clinical appearance during the past few thousand years because of climate, race, habits, diet, and other geographic factors.

Pinta is a distinct clinical entity belonging to this group of diseases, having many bacteriologic and serologic aspects that are similar to those found in yaws, syphilis, and bejel, but in other aspects there are differences. In a recent study of pinta, Rein[12] states that the bacteriologic and serologic characteristics of this disease would tend to corroborate the view of Hudson, in that this infection is similar in many ways to the other treponemal infections. There are other authorities, however, who disagree with Hudson's point of view. They believe that there are different races and species of treponemas, causing different and distinct diseases.

Similarities and differences in the treponematoses and the diseases they produce have been discussed briefly in order that we may have a better understanding of the response to the antibiotic therapy in this group of closely related clinical entities. It will be seen that the response to therapy is similar. Clinically the diseases in this group respond to treponemicidal agents including arsenic, bismuth, penicillin, oxytetracycline, and other antibiotics. Oxytetracycline has been found to be efficient in the treatment of several of the treponemal diseases.

Penicillin has been widely used in the treatment of syphilis, yaws, bejel, and pinta. The response to therapy with this antibiotic has been universally good. Mass therapy has been conducted successfully for treatment and control in many parts of the world. Penicillin given in an absorption-delaying menstruum, both in individual therapy and in treatment of large groups, is of great value in those countries that are largely rural and in situations in which the majority of patients must be treated with single injection schedules. Welch,[13] in a recent review of antibiotic therapy, points

out that although the various broad-spectrum antibiotics are effective in the treatment of certain treponemal diseases, the repository penicillin therapy is still the treatment of choice. Recent work, however, indicates that oxytetracycline is the drug of choice in the treatment of the late manifestations of yaws.

Although there has been no evidence of penicillin resistance in this group of organisms, such strains may be encountered. In case of resistance to penicillin or sensitivity of certain individuals, our second line of defense would be the broad-spectrum antibiotics. The value of oxytetracycline and other broad-spectrum antibiotics in the treatment of bejel and pinta must await further studies, even though preliminary reports are good.

Oxytetracycline has also been used in the treatment of other spirochetal diseases common in certain tropical areas. Hobby et al[14] found that oxytetracycline given in low dosage sterilized the blood of rats experimentally infected with *Borrelia recurrentis*, the organism producing relapsing fever in man. Attempts to find studies on the relative efficiency of the antibiotics in the treatment of this disease in man have failed.

There have been reports of satisfactory treatment of Weil's disease, caused by *Leptospira icterohaemorrhagiae* with oxytetracycline if therapy is started early in the course of the disease. The results obtained in clinical trials in vitro and in experimental infections in laboratory animals have been somewhat disappointing.

It is obvious that much more work must be done before the therapeutic status of oxytetracycline and other broad-spectrum antibiotics in the treatment of the various spirochetal diseases can be properly evaluated.

SUMMARY

The use of the antibiotics now available for the treatment of the so-called tropical diseases has been satisfactory in some types, disappointing in others. Oxytetracycline has been found to be effective against most of the spirochetal diseases and certain intestinal protozoa. Oxytetracycline is a highly effective agent in the treatment of all forms of intestinal amebiasis but ineffective in extraintestinal infections, especially amebic liver abscess with *E. histolytica*. Oxytetracycline has been used with some success in the treatment of pinworm infections in man. The other helminths, which are so important in certain tropical areas, do not respond to antibiotic therapy. Thus with the exception of the spirochetal diseases, intestinal amebiasis, and pinworm infections, other drugs are more effective against the animal parasites of man than the antibiotics. It is hoped that with the discovery of new antibiotics one will be found that will be active against certain animal parasite infections, such as schistosomiasis, for which no effective therapeutic agent is now available. In other parasitic infections we need therapeutic agents that are not only effective in removing the parasites but are less toxic and easier to administer than those drugs now available. Thus careful study of the efficiency of all antibiotics in the treatment of tropical diseases must continue.

BIBLIOGRAPHY

1. Most, H., and Van Ashendelft, F.: Laboratory and clinical observations on the effect of terramycin in the treatment of amebiasis, Ann. New York Acad. Sc. *53*:427, 1950.
2. Most, H., and Van Ashendelft, F.: Laboratory and clinical observations on the effect of terramycin in the treatment of amebiasis, Am. J. Trop. Med. *31*:284, 1951.
3. Tobie, J. E.; Most, H.; Reardon, L. V., and Bozicevich, J.: Laboratory results on the efficacy of terramycin, aureomycin and bacitracin in the treatment of asymptomatic amebiasis, Am. J. Trop. Med. *31*:414, 1951.
4. Killough, J. H., and Magill, G. B.: Terramycin in epidemic typhus, amebic dysentery, and typhoid, J. A. M. A. *147*:1737, 1951.
5. Elsdon-Dew, R.; Armstrong, T. G., and Wilmot, A. J.: Antibiotics and amoebic dysentery, Lancet *2*:104, July 19, 1952.
6. Frye, W. W.; Brooke, M. M., and Weinstein, P.: Antibiotics in the treatment of acute amoebic dysentery, Ann. New York Acad. Sc. *55*:1104, 1952.
7. Martin, G. A.; Garfinkel, B. T.; Brooke, M. M.; Weinstein, P. P., and Frye, W. W.: Comparative efficacy of amebacides and antibiotics in acute amoebic dysentery; used alone and in combination in five hundred and thirty-eight cases, J. A. M. A. *151*:1055, 1953.
8. Sappenfield, R. W.; Carter, F. R. N.; Culbertson, C.; Brooke, M. M.; Payne, F. M., and Frye, W. W.: Studies of a water-borne outbreak of amebiasis in South Bend, Indiana. II. Therapeutic aspects. J. A. M. A. In press.
9. Loughlin, E. H., and Joseph, A. A.: Terramycin in the treatment of yaws, Antib. & Chemo. *1*:76, 1951.
10. Loughlin, E. H.; Joseph, A. A., and Duvalier, F.: Oxytetracycline intramuscular in the treatment of yaws (Pian), Antib. & Chemo. *4*:155, 1954.
11. Hudson, E. H.: Treponematosis, Oxford Medicine *5* (Pt. 3):656 (9), 1946.
12. Rein, C. R.: Bacteriologic and serologic aspects of pinta, Am. J. Syph., Gonor. & Ven. Dis. *38*:336, 1954.
13. Welch, H.: Principles and Practice of Antibiotic Therapy, New York, Medical Encyclopedia, Inc., 1954.
14. Hobby, G. L.; Dougherty, N.; Lenert, T. F.; Hudders, E., and Kiselak, M.: Antimicrobial action of terramycin *in vitro* and *in vivo*, Proc. Soc. Exper. Biol. & Med. *73*:503, 1950.

Editorial Survey

Nutrition in Health and Disease

It is safe to say that for every patient who consults a physician for an infection, there is at least one other who requests advice on a problem of nutrition. Popular magazines have excited the public to be "nutrition-conscious," with the result that the long-suffering general practitioner is deluged with inquiries about vitamins, minerals, proteins, and amino acids. Confusion is heightened by the steadily increasing proportion of aged individuals in the population, many of whom suffer from some form of faulty nutrition.

NUTRITION AND AGING

There is little doubt that many of the chronic degenerative diseases of old age such as diabetes, cardiovascular dysfunctions, and arthritic conditions, are related to disturbances in nutrition and metabolism. For example, Brozek's[1] study on the changes in human body composition during maturity showed there is a definite increase in the fat content of the body with age, particularly in women. And this change is not always manifested in "bulges," as is popularly supposed; frequently there may be an occult increase of fat at the expense of muscle tissue.

Among older people, the problem of nutrition has a dual and seemingly paradoxic aspect. One section of that age group consists of the over-eaters who appear to find some compensation for disillusionment, loneliness, and a sense of insecurity in food. The other section complains of lack of appetite and confines its diet to easily ingested foods such as starches and sugars. In the first instance, a high intake of animal fats and cholesterol can contribute to atherosclerosis; in the second, protein starvation often leads to obesity, edema, and hepatic damage. In both instances, the physician is required to understand something of the patient's mental-emotional life before prescribing therapy.

PROTEINS AND AMINO ACIDS

The metabolism of ingested proteins is known to depend on enzymes and hormones. The administration of growth hormone enhances the storage of proteins, as was shown by Bartlett and Gaebler.[2] It is now also well established that certain of the testosterone esters appreciably improve the retention of nitrogen in body tissues. Protein malnutrition in aging people may thus be a natural consequence of their lowered production of certain androgenic hormones by the gonads and the adrenal glands. In such cases, an increased intake of food proteins would seem to be relatively useless because of the organism's inability to utilize them.

As regards the amino acids, it is to be expected that the general practitioner will have a worrisome time in the near future, due to a "popularization" of these elements in the lay press. There is no doubt that imbalance among amino acids in the diet can lead to nutritional disturbances, but in the present state of medical knowledge it would be a bold biochemist who could confidently lay the blame on one amino acid rather than another. As was shown by Rose and co-workers,[3] the accepted

distinction between so-called essential and nonessential amino acids may not be as valid as was supposed.

SODIUM VALUES

The low sodium diet has become increasingly popular in the treatment of congestive heart disease, hypertension, ascites, and certain manifestations of edema. A number of controlled studies certainly support the value of sodium restriction, although results in the treatment of hypertension are as yet inconclusive. Kempner and his colleagues[4] published encouraging results in treating hypertension with the "rice diet," but these findings have not been consistently supported by other investigators.

In any case the restriction of sodium should be approached with some caution. When a patient's renal and sweat mechanisms are normal, the conservation of sodium is usually unimpaired. But it is in patients with congestive heart failure or with chronic nephritis that one finds the renal dysfunctions that cause a poor retention of sodium. In such cases, depletion of dietary sodium may induce oliguria, edema, cramps in the extremities, and even death.

This problem has been further aggravated in recent times by the public's immoderate demand for the adrenocortical hormones to combat arthritic diseases. The physician is deluged with demands for the "wonder drugs," cortisone and ACTH, although he is well aware that both these hormones induce sodium retention during the initial stage of therapy.

VITAMINS AND MINERALS

Progress continues to be made in understanding the metabolic role of various vitamins. Synthetic vitamin A may now be safely given to children who are intolerant of fish liver oils. Riboflavin is being studied intensely for its possible connection with such baffling conditions as psoriasis. Nicotinic acid deficiency, according to some studies, is associated with pellagrous dermatitis, glossitis, diarrhea, and mental depression; and nicotinic acid compounds are being studied in the psychoses of senility, joint mobility, dysmenorrhea, pruritis, and hyperkeratosis. Folic acid and vitamin B_{12} continue to occupy the attention of numerous investigators, particularly in the field of blood dyscrasias and cancer.

Minerals are also receiving a share of attention in problems of nutrition, though here the extent of knowledge is fairly limited. The place of iron in blood metabolism is well known, but an explanation must yet be given for the occurrence of so many acute infections accompanied by hyperferremia. The role of copper in human metabolism and the function of cobalt and zinc are still not clear. Hypocupremia has been identified in chronic infections and it occurs in many neoplasms; there is also some evidence that serum zinc is reduced in most acute infections. Beyond these findings little more is known.

REFERENCES

1. Brozek, J.: Federation Proc. *11*:784, 1952.
2. Bartlett, P. D., and Gaebler, O. H.: J. Biol. Chem. *196*:11, 1952.
3. Rose, W. C.; Burr, W. W., and Sallach, H. J.: J. Biol. Chem. *194*:321, 1952.
4. Kempner, W.: Am. J. Med. *4*:545, 1948.

GENERAL PRACTICE CLINICS

This new monthly section of General Practice Clinics features reports of papers delivered at current medical meetings in the United States and abroad.

Progress in the Clinical Diagnosis of Poliomyelitis

Presented by RUSSELL J. BLATTNER, M.D. (Baylor University College of Medicine), before the American Medical Association, San Francisco, June 24, 1954.

The difficulty in making a definite diagnosis of poliomyelitis, particularly early in the clinical course, is shown in the fact that during the period from June, 1950, to February, 1954, 151 of the total of 994 patients admitted to the Southwestern Poliomyelitis Respiratory Center were proved not to have acute poliomyelitis. Among the many diseases which must be differentiated from polio are meningoencephalitis, encephalitis of undetermined origin, hysteria, infectious neuritis and acute upper respiratory tract infections.

There are four types of poliomyelitis. The silent type causes no problem as there are no symptoms or signs. The abortive type may resemble a common cold and usually bed rest alone is all that is necessary. The two types presenting the greatest problem are the paralytic and non-paralytic varieties of the disease. The non-paralytic form is usually characterized by some degree of nuchal rigidity, vomiting, drowsiness, leg aches, and possibly constipation. It is often difficult to evaluate nuchal rigidity in a child, especially an uncooperative one. One should evaluate the attempts of the child to sit up, test flexion of the head to chest or "kissing the knees" and the Kernig and Brudzinski signs. By placing fingers on the spinal processes as the patient attempts to bend, it is possible to feel the difference in the separation of the processes. The back may feel poker-like in contour. This form of the disease is also characterized by hyperesthesia, muscle tenderness, and absence of cremaster and upper and lower abdominal reflexes. A lumbar puncture should be done.

In the paralytic type of poliomyelitis, changes in deep reflexes, either increasing or decreasing, forewarn of the onset of paresis or paralysis. The distribution of paralysis is asymmetrical and spotty. Once the diagnosis has been made, the question is whether the process will progress, and especially whether the respiratory mechanism will be involved. Other characteristics of this type of the disease are a flushed face with perioral pallor and persistent but not high fever. A septic temperature is not characteristic. The patient may appear more apprehensive than is usual, and there may be cortical hyperirritation and jerky twitches and muscle fibrillation. Nystagmoid movements of the eye have been noted which are actu-

ally an inability to focus and are not constant. The progress of the disease occurs during the febrile period and is usually over at least 48 hours following the fall of the temperature.

A close watch must be kept for signs of serious complications such as any change in the voice, increasing ineffectual cough, difficult swallowing, and involvement of the deltoid muscles or cranial nerves. Involvement of the respiratory center is characterized by hyperthermia, hypertension, cardiac arrhythmias and peripheral vascular collapse. The effects of hypoxia and CO_2 retention from faulty mechanical breathing devices, or mismanagement of them, should be watched. Restlessness, dyspnea, cyanosis, pallor and circumoral twitching are some of the signs that are seen.

Nutrition in Congestive Heart Failure

Presented by M. D. WOHL, M.D., AND C. R. SHUMAN, M.D., before the American College of Cardiology, Third Interim Scientific Meeting, Miami Beach, Florida, November 11–13, 1954.

Nutrition Management. The authors outlined requirements of nutrition regimen: reduce heart work load, and maintain calories, nitrogen, vitamins and minerals at level necessary for individual patient. In *acute* cardiac failure, the Karrell milk diet is valuable and should be used for as long as four days. The diet: 600 calories of skimmed milk and a little less than 1 Gm. of salt. Sodium should be kept below 600 mg. Multivitamin supplements should be given from the first day. In patients with recurrent chronic heart failure, the maintenance of nutritional balance centers around (a) replacement of existing depletion of body stores and (b) restoration of deranged myocardial metabolism.

Loss of body protein is often overlooked in cardiac failure. With alteration in protein metabolism, heart failure may become refractory to treatment. This calls for high protein intake with a minimum of salt. Furthermore, it was found that in chronic cardiac failure there is a greatly reduced *thiamine* and *cocarboxylase* content of tissues. This may prevent utilization by myocardium of carbohydrate derived substrate for energy production. This may result in a rise of blood lactate and pyruvate which may further reduce cardiac efficiency and render maintenance of compensation more difficult. Thiamine supplementation, preferably parenterally, should be given attention.

Mineral Disturbances. There is biochemical evidence of increased sodium and decreased intracellular myocardial potassium in cardiac failure. These intracellular ionic shifts may inhibit the enzyme system regulating the energy transfer from glycolysis to the contractile machinery. In addition to digitalis the use of potassium salts may be necessary to restore normal high intracellular potassium and low sodium levels. It is realized that when biologic and morphologic changes in myocardium become irreversible, nutritional repletion in the patient with advanced failure is an almost unattainable goal.

Quarterly Review of OPHTHALMOLOGY

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INCORPORATING INTERNATIONAL RECORD OF OPHTHALMOLOGY

FOREWORD

The objective of the QUARTERLY REVIEW OF OPHTHALMOLOGY is to bring together in one publication concise but authoritative abstracts of current articles on ophthalmology, according to an all inclusive plan which includes all special, state, and national journals as well as the bulletins of clinics, hospitals, etc., and the transactions of meetings. This embraces both the domestic and foreign literature.

To assist the reader to locate quickly the articles of current interest all data are classified and published according to the following systematic plan:

Anatomy, Embryology, Heredity, Development and Nutrition

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Anomalies of Refraction and Accommodation, Contact Lenses

Conjunctiva

Cornea, Sclera and Tenon's Capsule

Anterior Chamber and Pupil

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Miscellaneous

Book Reviews

Announcements

A section entitled International Record of Ophthalmology is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

ABSTRACTS

ANATOMY, EMBRYOLOGY, HEREDITY, DEVELOPMENT AND NUTRITION

1. *Heredity and the Eye.* CONRAD BERENS. Eugenics Quarterly *1*:16, June 1954.

What are the probabilities of an abnormality with which one or both of the parents are affected, appearing in the offspring? What abnormalities are inheritable and what are the chances of an abnormality appearing in more than one offspring? The author has made an attempt to answer these and similar questions in so far as they are related to the eyes and adnexa.

After briefly reviewing statistical data, revealing the need for more adequate records, he explains the theory of heredity based on chromosomes, genes, dominant, recessive and sex-linked inheritance, in a way easily understandable to a layman. Doctor Berens then proceeds with the description of inheritable anomalies starting with those affecting ocular adnexa through errors of refraction and muscle anomalies to coats of the eye, intraocular structures and the optic nerve.

He does not hesitate to admit our very incomplete knowledge of genetics and points to continued research as the only way to better understanding of this most important subject both from the medical and social point of view.

OCULAR MOVEMENTS AND MOTOR ANOMALIES NYSTAGMUS READING DISABILITY

2. *Treatment of Paralysis of the Extra-Ocular Muscles.* H. REED. Canad. M. A. J. *70*:628–631, June 1954.

Congenital ocular muscle palsies often are overlooked and occur more frequently than is generally realized. The vertical muscle imbalance may be compensated, may lead to a head tilt or may produce a manifest squint. Acquired muscle palsies may come on suddenly, they produce the symptoms of vertigo, giddiness, and confusion. The diagnosis is made by examination of the eyes in different positions of gaze and by such aids as the Hess and Lancaster screen tests. A careful history and examination for possible causes of the acquired palsy are indicated.

Traumatic cases improve over a period of four months or even one year. After improvement stops surgical measures can be undertaken.

Twenty-five cases are presented in table form. 1 reference.

ANOMALIES OF REFRACTION AND ACCOMMODATION, CONTACT LENSES

3. *Contact Lenses: Statistical Evaluation of Tolerance.* R. SATTLER. Klin. Monatsbl. Augenh. *125*:215, 1954. (In German.)

According to Sattler two factors are of primary importance in the tolerance for adherent or contact lenses: irritation resulting from mechanical factors, and foggy vision or "Sattler's veil" which result from edema of the corneal epithelium. When this foggy vision appears other unpleasant sensations often subside, possibly because the pain receptors of the cornea become less sensitive after the edema develops. Questionnaires regarding tolerance for contact lenses were sent to 1,100 persons for whom such lenses had been fitted, and replies were received from 365. Seventy-one (19.5 per cent) stated they were not wearing their contact lenses; 213 (58.3 per cent) wear them every day, and 81 (22.2 per cent) wear them occasionally. Seven hours is the average period for which they are worn. Age, sex, or occupation seem to exert no great influence, but the indications for which the contact lenses were prescribed seem to influence the tolerance. Patients with medical indications, such as those with keratoconus, irregular astigmatism, unilateral aphakia, or severe myopia in general tolerate their contact shells better than do some of the others. Those who wear them because of "social indications" (professions or sports) seem to become better adjusted to their use than those in whom appearance (vanity) was the only reason for preferring contact to other lenses. The author knows of one patient who has worn contact lenses for 21 years, 20 patients who have worn them over 10 years, 63 longer than five years, and 141 longer than three years. The others have worn them for from one to three years. Irritation of the conjunctiva is a much more frequent cause of complaint than is epithelial edema of the cornea. The danger of a corneal erosion is slight in the case of contact lenses with nonspherical scleral part, which are the only ones under consideration here, provided that all precautions are followed during fitting and adjustment.

4. *The Design and Development of a Contact Lens for Underwater Seeing.* C. NAGEL. Am. J. Optometry *31*:468, September 1954.

A contact lens was developed for the armed forces with a plane front surface for improved vision under water. It was found to have advantages over the faceplate now used.

5. *The New Contact and Corneal Lenses.* MAURICE W. NUGENT AND CONRAD BERENS. Today's Health *32*:26, September 1954.

This article was written at the request of the American Committee on Optics and Visual Physiology and deals with the history of the contact and corneal lenses.

In abstract, the authors explained the difference between contact and corneal lenses as well as lenses requiring fluid and those that do not. The article emphasized that the fluidless lenses, although still not perfect, still have the greater promise insofar as useful wear is concerned.

Who should wear this type of visual aid was also considered and it was stated that the greatest requirement from an ophthalmologic standpoint was for those who need such a visual aid because of corneal abnormalities. However, it was also stated that such devices should also be considered for high refractive errors and from the cosmetic viewpoint as well.

The history of corneal and contact lenses was outlined to some degree and goes back to the year 1508 up to the present time. Special note was given to the fact that Kevin M. Touhy developed the first successful plastic fluidless corneal lens in 1947.

The dangers of the use of corneal and contact lenses were also considered with the main emphasis in regard to the fluidless lenses being on minute corneal abrasions. The authors however stated that in their experience these were of no great significance, as they healed promptly if and when they occurred, providing the patient was logical enough to remove the lenses in the presence of irritation. The importance of loose eyelids was emphasized also as this has a great deal to do in the length of time such devices can be worn. It is obvious that if the lids are loose, then the lens is not hugged to the cornea by reason of varying degrees of blepharospasm. This, of course, permits better circulation of lacrimal fluid beneath the lens and helps to protect the cornea as well.

The percentage of patients that can successfully wear these lenses was also remarked upon and the authors felt that the new fluidless type of lenses causes less irritation and blurring and gave much better wearing time, so that about one-third of all those fitted with these lenses can wear them for at least a special purpose and it was also stated that approximately one-third can wear them to the exclusion of spectacles. This, of course, means that one-third of the patients fitted cannot wear them at all. However, two-thirds can at least obtain satisfactory wearing time and it would seem therefore such effort and expense are justified.

The cost was also stated as being variable between $150 and $300, and that such cost was not likely to be lower because of the time required in measuring, fitting and in follow-up rechecks.

Probably the most important part of the paper was the part which asked for repeated observation of these patients for lengthy periods of time following their purchase, so that the eye could be studied and protected until more is known regarding the safety of these new devices. It was emphasized that the ophthalmologist should use Fluorescein and biomicroscopy at all follow-up visits and that if any significant abrasion occurred, then the lenses must be removed. Patients were also advised that it was the duty of the ophthalmologist to specify the type of lens required for the individual's eye and that his knowledge would be the important factor in deciding what type of lens should be prescribed.—*Author's abstract.*

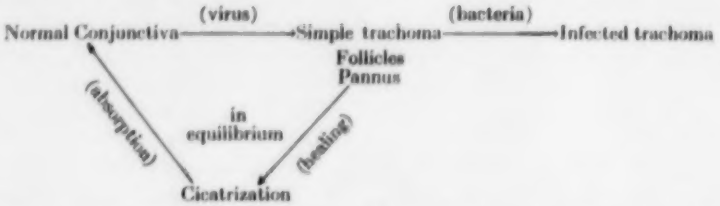
CONJUNCTIVA

6. *A New Trachoma Concept.* RENALD CHING, Hong Kong, China. Arch. Ophth. *51*:750–761, June 1954.

Trachoma is a mild, insidious disease, frequently self-limiting, not especially infectious, comparatively harmless, the causative organism of which we accept

today is a filterable virus, not yet isolated, but believed to be specific for conjunctival and corneal epithelium.

There are only two types of trachoma—simple and infected. The pathology of simple trachoma is a quiet hyperplasia of the lymphatics. It is not an inflammation; therefore it is not a conjunctivitis. There is no acute phase, and the time and mode of onset are unknown. A carrier state is possible. It never causes blindness. In fact, seldom is there even any irritation. The primary lesion is a follicle, which microscopically looks like any other conjunctival follicle. An equilibrium is established:



A characteristic of trachoma is the continuous shifting of this equilibrium, which is influenced by a number of factors not yet all quite clear to us. These factors may increase the virulence of the virus and cause the appearance of more follicles, or they may raise the defense power of the host tissue so that healing and absorption take place. The invasion of a secondary organism will cause a marked disturbance in the equilibrium—even to breaking it up and changing it into a different pathological product, to be called infected trachoma. Antibiotics and sulfa drugs do not seem to have much effect on this equilibrium.

Diagnosis of trachoma is based essentially on three clinical signs. They are: (1) follicles, 30 per cent; (2) cicatrices, 30 per cent; and (3) pannus, 40 per cent. The percentages are arbitrarily put down to indicate the certainty of diagnosis. There must be at least 60 per cent certainty to make the diagnosis stand. Any single finding is not trachoma. All three make trachoma with 100 per cent certainty, and any two together can pass on trachoma with a certainty of 60 per cent or 70 per cent. Pannus is given a 40 per cent value because it is considered that much more pathognomonic of trachoma. Trachoma can exist without pannus, but the diagnosis becomes doubtful indeed.

The criterion of trachoma cure is likewise considered when the triad signs are broken up so that less than 60 per cent of points can be given. When two of the three cardinal signs have been removed, the diagnosis can no longer stand on the remaining leg. Usually all three signs disappear in the cure of simple trachoma, and a normal conjunctiva is left. In infected trachoma, the criterion of cure is essentially the subsidence of inflammation, which then converts it into simple trachoma, but some scarring will be left behind according to the duration and intensity of the infection.

Infected trachoma is an entirely separate entity. This is the trachoma described in textbooks and writings, and usually seen in clinics. Simple trachoma and infected trachoma differ distinctly in etiology, pathology, symptoms and treatment.

We have heretofore not given this distinction adequate thought, a fact which explains the confusion in the trachoma literature of the past. Infected trachoma can be changed into simple trachoma by the use of antibiotics and sulfa drugs. Likewise, simple trachoma becomes infected trachoma when a secondary infection is present.

This paper gives a detailed discussion of the trachoma triad. It suggests a uniform, simple method of how to record trachoma cases for the purpose of study, research, and practical use. The application of this new trachoma concept in public health and quarantine problems is mentioned. 17 references. 1 table.—*Author's abstract.*

CORNEA, SCLERA AND TENON'S CAPSULE

7. *Malignant Melanoma of the Cornea.* WINDSOR S. DAVIES, Detroit, Mich., AND W. H. BAILEY, St. Louis, Mo. Arch. Ophth. 52:923–924, December 1954.

This was a report of a case of malignant melanoma arising in the cornea; serial sections were made of the entire cornea. The tumor apparently arose from the basal cells of the corneal epithelium as shown by marked activity of these cells on one side of the tumor. This activity, however, ceased as the region of the limbus was approached. 1 reference. 3 figures.—*Author's abstract.*

RETINA

8. *Motions of the Retinal Image during Fixation.* LORRIN A. RIGGS, Providence, R. I.; JOHN C. ARMINGTON, Washington, D. C., AND FLOYD RATLIFF, Cambridge, Mass. J. Optic Soc. America 44:315–321, April 1954.

The ability of an observer to maintain steady fixation on a test object is limited by involuntary eye tremor. Such tremor is characteristic of balanced muscular systems such as those serving to rotate the eye. Rotations of the eye cause proportional displacements of the retinal image of a stationary test object. Data are given for typical excursions of the retinal image during various exposure intervals from 0.01 to 1 sec. in duration. The data show that under good experimental conditions the retinal image is virtually stationary for exposures up to 0.01 sec. in duration.

Many visual experiments have involved short flashes of up to 0.1 sec. duration. The data given indicate that during this time the retinal image typically moves through a distance corresponding to 25 sec. of arc, approximately the diameter of a single retinal cone. Thus it might be said that 0.1 sec. is often a practical exposure time for the control of eye movements and 0.01 sec. is an exposure time which nearly always results in a "stopped" retinal image. 19 references. 12 figures.—*Author's abstract.*

9. *Diathermic Treatment of Different Forms of Retinal Detachment and Results.* H. WEVE. Tr. Ophth. Soc. Australia *13*:95–100, 1953.

This short paper comprises an analysis of parts of Professor Weve's vast series of detachment operations. He found that the ratio of men to women was consistently 3:2 and the right eye is more often affected than the left in the ratio of 11:10. Only 54.5 per cent of patients were myopic, 8 per cent were aphakia, 10 per cent were traumatic, and 31 per cent were so-called senile. Operation within the first week of occurrence of the detachment is most important. A plea is made that retinal detachment should not be an operation performed by all ophthalmic surgeons. It is suggested that patients should be sent to centers where there are experienced surgeons and adequate facilities.

10. *Vascular Disturbances in the Retina of Diabetic Patients.* ERNST HEINSIUS. Klin Monatsbl. f. Augenh. *125*:1–5, 1954.

This is a summary of the author's impression after having examined more than 2,000 diabetic patients.

There is first of all the true diabetic retinopathy with capillary aneurysms. There are also arteriolar sclerotic changes with yellow-white areas of retinal degeneration. This second form is as frequent in diabetic patients as the true diabetic retinopathy. Finally there are changes in the veins with smaller and larger thrombi. The important factor in the development of the lesions is the duration of the diabetes and the most important treatment is the regulation of the diabetes. Local treatment (vasodilators, anticoagulants) is sometimes of value.

11. *Clinical and Therapeutic Considerations of Detachment of the Retina.* GIOVANNI RAMA. Rassegna ital. d'ottal. *23*:189, May-June 1954.

In the first part of the paper the author reviews and discusses the pathogenetic significance of the fundamental clinical data observed in cases of retinal detachment in his clinic during the last three years. In the second part he presents the therapeutic orientation of his school. He expresses the opinion that surgical intervention must be attempted even when the probability of success is slight. Indications, technical method employed, and factors which permit prognostic judgment and treatment are explained. He emphasizes that the technic must not be standardized but adapted to the individual problem. Preventive surgery is also discussed.

12. *Macula: Alteration of the Vascular Arrangement in Arteriosclerosis.* J. LIJO PAVIA. Rev. oto-neuro-oftal. *29*:65.

The author bases his findings on his work reported in October 1952, "Fundus of the eye in the experimental hypercholesteremia," which he considers as the first part of his studies on arteriosclerosis.

He considers essential the ophthalmoscopic sign of arteriolar constriction with manifestations in the macular area. (He considers as macula the region the size of 1 disc diameter including the fovea.)

The methodical arrangement and alternate disposition of arterioles and venules crossing the macula in radiating manner extending to the margin of the fovea, is the arrangement No. 1 of "vascular normal" in the macula. As the arteriolar constriction accentuates, the arterioles are gradually obstructed and as they do not contain blood they are invisible and one sees only the small veins in the center of the macula (arrangement No. 2), arteriosclerosis of second degree.

When the process of sclerosis and hypertension is more advanced, the arterioles are invisible within one disc diameter of the limit of the macula and the small veins are seen in the center of this area and appearance corresponds to the arteriosclerosis of the retina and choroid of second degree, in which the process is reversible, according to the author.

13. *Cerebral Vessels and Retinal Vessels.* J. LIJO PAVIA. Rev. oto-neuro-oftal. *29*:75.

The author bases his work on the proposed concept by Bailliart that the finding of vascular lesions must represent similar alterations in the cerebral vessels. He refers then to the aneurisms of the cavernous sinus and thrombosis of the carotid, illustrating the vascular relations of the brain with the eye by means of schema combined from Penzholz, Mildraed and Fischer. Afterwards he establishes the relation between humeral minimum pressure and diastolic pressure of the central artery of the retina, and the observation of edema of the papilla in cases of endocranial hypertension.—*Author's abstract.*

14. *Effect of Oxygen on Developing Retinal Vessels with Particular Reference to the Problem of Retrolental Fibroplasia.* NORMAN ASHTON, BASIL WARD, AND GEOFFREY SERPELL, Univ. of London, London, England. Brit. J. Ophth. *38*:397–432, July 1954.

This paper reports the full experimental details of an extensive investigation of the influence of oxygen on the developing retinal vasculature of the kitten. High concentrations of oxygen at atmospheric pressure are able to induce in these vessels a type of vasoconstriction which progresses to complete obliteration. This newly described phenomenon was not seen in extra-ocular vessels and was apparently confined to the developing retina.

It was found that the extent of vaso-obliteration was inversely proportional to the maturity of the vessels, and once the retinal vasculature was fully mature, obliteration could not be produced. It was directly related to the duration of exposure, taking about 36 hours to obtain total obliteration in the most sensitive age groups. It was directly related to the concentration of oxygen; concentrations below 35 per cent had little or no effect on the most sensitive age groups.

This vaso-obliterative effect of oxygen is the basis of the pathological events which subsequently occur, for when the animal was returned to air, after several hours of oxygen exposure, the vessels were unable to re-open, due to intravascular coagulation or adhesion of the vessel walls, and the retina was without an adequate blood supply. A profuse and disordered neovascularisation then developed, pro-

ducing a pathological picture exactly analogous to the early stages of retrolental fibroplasia.

Several factors which might influence the above course of events were studied and it is particularly interesting to note that Tromexan profoundly modified vaso-obliteration; this was thought to be due to the prevention of intravascular coagulation so that affected vessels were able to reopen in air. The probable mechanisms involved in the vaso-obliterative and vaso-proliferative phases are discussed.

Relating these experimental results to retrolental fibroplasia, the authors conclude that the findings exactly parallel the early stages of the human disease; the difference in the subsequent course is dependent upon the development of retinal detachment which did not occur in the kitten experiments. Despite this difference the two diseases appear identical in origin and an urgent plea is made for the control of oxygen therapy in the treatment of the premature baby. 52 references. 30 figures. 4 tables.—*Author's abstract.*

15. *Direct Observation of the Effect of Oxygen on Developing Vessels (Preliminary Report).* NORMAN ASHTON AND CHARLES COOK, London, England. Brit. J. Ophth. *38*:433–440, July 1954.

It was recently discovered that high concentrations of oxygen are able to exert on growing retinal vessels a peculiar type of constricting action which progresses gradually to complete obliteration of the ingrowing complexes (Ashton, N.; Ward, B., and Serpell, G. (1953) Brit. J. Ophthal. *37*:513). This paper reports preliminary experiments designed to elucidate the problem further.

It was found that hyperoxia has no effect on growing vessels in the rabbit cornea or in the rabbit ear chamber and that chick embryos may survive 80 to 90 per cent oxygen during the last seven days of incubation, hatch out alive, and develop normally in air.

The authors describe a new technic which permits direct observation of the effect of oxygen on the retinal vessels of the living animal. Oxygen had no observable effect on the retinal vessels of the adult cat but in the kitten *immediate* and *delayed* reactions were seen. The former consisted of vaso-constriction and capillary obliteration developing after five minutes exposure to oxygen. This did not progress to total obliteration and the vessels reopened after about 10 minutes and remained in this state for about five and one-half hours when the delayed effect came into operation. The vessels then again constricted and total vaso-obliteration gradually developed, becoming complete in about eight hours. Once this state was achieved the circulation could be opened or closed in about five minutes by alternating air and oxygen.

Vaso-obliteration could not be induced in the detached retina, and obliterated vessels reopened when detachment developed. 3 references. 8 figures.—*Author's abstract.*

16. *Pathological Basis of Retrolental Fibroplasia.* NORMAN ASHTON, London, England. Brit. J. Ophth. *38*:385–396, July 1954.

The features of the late stages of retrolental fibroplasia are generally agreed upon and this report, therefore, is mainly concerned with the earlier stages of the disease. The pathological features of four representative cases are described in detail and the conclusions are in accord with the widely accepted view that retrolental fibroplasia is a primary retinal disease of noninflammatory origin, which results from disordered vascularization. Its development and course may be simply stated in three pathological stages—(1) Proliferation of vasoformative tissue into the vitreous. (2) Commencing retinal detachment and the formation of fibrous strands in the vitreous. (3) Extensive retinal detachment with the formation of a dense retrolental fibrous membrane followed by late atrophic changes.

Since the basis of the disorder is merely an aberrant overgrowth of the developing retinal vessels it is not improbable that there may be a variety of precipitating causes, but the vast majority of cases consists of premature babies who develop the disease post-natally in relation to oxygen therapy. There would thus be good grounds for applying a special name to the oxygen-induced disease, but it is suggested that a revision of nomenclature should await further clarification of the problems of pathogenesis. 14 references. 14 figures.—*Author's abstract.*

EYELIDS

17. *Correction of Upper Lid Blepharochalasis.* MOREY L. PARKES, Hollywood, California. Eye, Ear, Nose & Throat Monthly *33*:349–350, June 1954.

A method is described for the correction of upper lid blepharochalasis that will overcome not only redundant upperlid tissues but also redundancy that exists immediately above the lid beneath the eyebrow. This method enables the operator to "lift" the tissues lateral to the upper lid as well.

An incision is made about 2 mm. below the eyebrow and the necessary amount of skin is resected. Care is needed to make the dissection superficial enough to spare the nerve supply in this area. 4 figures.—*Author's abstract.*

ANESTHESIA

18. *Curare in Ophthalmology.* SHEILA KENNEY. Tran. Ophth. Soc. Australia *73*:679, 1953.

The use of curare produces relaxed muscles and an immobile eye under light anesthesia with early return to consciousness. The disadvantage is a tendency to increased bleeding. This can be controlled with the proper position of the patient before starting the anesthetic. Curare with local anesthesia was found to be particularly beneficial. Good palpebral and global akinesia preserves the ability of the patient to move the eye on command, and affects respiration as little as possible. One to 2 grains of luminal are given the night before and again two hours before

surgery. Atropine is given one hour before surgery to prevent salivation which may occur with curare. If the ocular tension is raised, a retrobulbar injection of procaine solution is given. The injection of curare into a vein on the back of the hand is begun when the local anesthetic is given (1 mg. tubocurarine per 14 pounds body weight). Injection is continued until ptosis is produced (usually after 3 mg.) and more is given as needed to aid relaxation. The hand grip is a useful guide to dosage. It is important to wait three full minutes after the last injection to avoid any interruption due to untoward reactions occurring during operation.

MEDICAL OPHTHALMOLOGY

19. *The Relationship Between the Severity and Care of Diabetes Mellitus and the Incidence of Diabetic Retinopathy.* P. B. LANDABURU. Arch. oftal. Buenos Aires *29*:7–21, January 1954.

A careful statistical analysis of 100 patients who were known to have had diabetes mellitus for no less than 10 years leads the authors to believe that, all other factors being equal, retinal changes are more apt to occur in poorly treated patients than in those submitted to prompt, efficient treatment, adequate from the start and continued without intermissions. 12 tables. 7 charts.

20. *Numerical Evaluation of Ocular Signs of Essential Hypertension.* HENRY MINSKY. Mt. Sinai Hosp. J. *21*:29–37, May-June 1954.

The author sought to establish a classification based on objective signs of hypertension in the eye. He divided the arterioles into branches or segments topographically, noting that narrowing is obvious only when the ratio of the arteriole to its branch is 10:6 or less. The signs were classified under optic nerve head, retinopathy, arteriolar narrowing, venule narrowing, and abnormality of the arteriovenous crossing. A code was devised to record the type, location, and degree of each finding. Each sign then was given a weighted value. The sum of all the signs' values after careful examination was then multiplied by a constant, which resulted in the diastolic pressure. It was believed that these calculated values for diastolic pressure were dependable for base line estimations; so much so that a calculated pressure less than the sphygmomanometric reading might indicate that the latter was raised because of psychogenic stimulation, and a calculated pressure greater than the sphygmomanometric reading might indicate that the latter was misleadingly low because of cardiac dysfunction.

ILLUMINATION AND ILLUMINATING ENGINEERING

21. *The Effect of Veiling Luminance upon the Apparent Brightness of an Object.* GLENN A. FRY AND MATHEW ALPERN. Am. J. Optom. & Arch. Am. Acad. Optom. *31*:506–520, October 1954.

A patch of veiling luminance superimposed on a bright object in a dark field reduces the apparent brightness of the object.

It has been shown that the effect obtained with a patch of veiling luminance extending 0.25 degrees beyond the boundary of the test object is approximately the same as for patches of much greater extent.

A retinal mechanism has been postulated to account for the effect similar to that previously postulated to account for contrast effects at borders. The principal feature of this mechanism is the transmission of an effect from one part of the retina to an adjacent part where it inhibits activity initiated by photoreceptors.

MISCELLANEOUS

22. *Reading—A Developmental and Educative Process.* ELIZABETH A. SIMPSON. Am. J. Optom. & Arch. Am. Acad. Optom. *31*:240–245, May 1954.

Although reading may have different meanings to different people, it is generally recognized as the most important aspect of communication. It is the primary link between the individual and all printed sources of knowledge and information. Through reading one increases his understanding of the world in which he lives as well as his understanding of himself. Reading also provides the primary means for continuous self-improvement; it is an important leisure time activity of both children and adults. For some individuals reading may become an escape at times. It is a well-established fact that academic success at all levels of education is primarily dependent upon reading proficiency; therefore, reading means academic success to some persons. Clearly, these concepts only explore a small portion of the many interpretations people place on the role of reading in their lives.

As the individual develops, his reading habits should also show signs of maturation and progress. To develop mature reading practices is a long range evolutive and educative process that is an important part of the individual's total growth. Through years of research and experience, psychologists and educators are now better able to understand the nature of the reading process that was formerly conceived of as the rather limited process of being able to look at a word and say it correctly.

23. *A System of Communication in Occupational Optometry.* RICHARD FEINBERG. Am. J. Optom. & Arch. Am. Acad. Optom. *31*:180–186, April 1954.

The technics for reciprocal communication between management and the optometrist, management and the employee, and the optometrist and patient are outlined. Check-list forms are presented to facilitate the transmission of information. By such means the optometrist's participation in the occupational vision program is assured. Another significant result is that a more complete service to management and the employee-patient will be assured. The sample forms presented are not copyrighted.

24. *Education for Survival.* DAVID D. MICHAELS. Am. J. Optom. & Arch. Am. Acad. Optom. *31*:187–191, March 1954.

An analysis of the professional status and prestige standing of individuals reveals that these depend to a great extent on the prestige of the profession as a whole. This, in turn, is conditioned by the quality and facilities of the optometric educational institutions that provide new members for the group. The effectiveness of the teaching program often determines whether the new graduate will become an asset or a liability to the profession and, consequently, influence the prestige status of every person in it. From this viewpoint, the general support and encouragement of optometry schools and their faculties is nothing more than enlightened self-interest. A summary of the progress made by the schools is encouraging, but continued and extended support is vitally needed. A number of definite suggestions are made, based on this review, by which every member of the profession can participate in maintaining and advancing undergraduate and graduate optometric educational standards.

25. *A New Buried Morable Orbital Implant.* JOHN H. KING, U.S.A.F. Med. J. *5*:835, July 1954.

The author used a modification of the Lee Allen implant in 67 cases with good result. The anterior surface of the implant is covered with a stainless steel mesh. Sutures are tied separately over the mesh of the implant.

26. *A Registering Low-Level Photometer.* W. E. KNOWLES MIDDLETON. Ottawa, Canada. J. Optic. Soc. America *44*:303–305, April 1954.

Because of the Purkinje effect, it is much better to use visual methods for photometry in the mesopic and scotopic ranges. A compact hand-held photometer has been designed for this purpose, which makes it possible to record about 60 readings without removing one's eye from the eyepiece of the instrument.

This is achieved by using a circular optical wedge as the measuring element, coupled mechanically with a circular disc on which a chart is mounted. A needle, which may be advanced radially between observations, is caused to pierce the chart when a balance is obtained.

Filters in a revolving turret give the present instrument a range of 5×10^{-2} to 2×10^{-6} cd.m^{-2} (1.5×10^{-2} to 6×10^{-6} millilambert). 6 references. 3 figures. —*Author's abstract.*

27. *School Lighting and Posture.* W. ALLPHIN. Illum. Eng. *49*:192, April 1954.

This investigation was made at the Bowditch school, Salem, Mass., a building which has one section 86 years old and another 45 years old, both undergoing a gradual program of modernization. At the time of the study some rooms had movable desks of light color and others had dark stationary furniture; all walls were painted in light colors, and artificial lighting from enclosed globes provided low illumination levels.

Unposed photographs were taken of children in grades one through eight during writing periods; 19 representative pictures are included in the paper, showing the writing postures assumed by the children. No relation could be shown between posture and illumination levels, direction of light, or glare. Tilting and twisting are apparently caused by bringing the eyes close to the work. The closeness, when it occurs, may be related to the following factors: the desk may be too high, the pen or pencil may be held so close to the point that the head must be tilted to see under the hand, a young child who is very intent upon his writing may get closer and closer to his work, "simply because there is no reason not to."

28. *Clinical Experience with Hard Resin Lenses.* GRANT BALDING AND WILLARD BALDING, Pasadena, California. Eye, Ear, Nose & Throat Monthly *33*:677, November 1954.

Advantages and disadvantages of hard resin lenses were compared to glass by the authors, based on their experience with the resin lenses over a four and a half year period. The disadvantages are cost, susceptibility to scratching, and use of large sizes and unusual shapes. The first two disadvantages are economic, the third optical, because the index of refraction is less than glass. The advantages are lower specific gravity, lowered refractive index, more resistance to fogging, increased light transmission, uniform absorption of color, and safety. High corrections, particularly in green colored glasses, are desirable. Strong green myopic lenses in hard resin have very few concentric rings. Hard resin lenses are particularly recommended for children, aphakics, and one-eyed individuals.—*Author's abstract.*

BOOK REVIEWS

Travaux d'Anatomie Pathologique Oculaire. F. HERVOUET. 186 pages (French). Masson & Cie, Paris, France.

This is a collection of 16 articles based on anatomopathological studies conducted at the Laboratory of the Eye Clinic in Nantes (Prof. G. P. Sourdille, Director). The majority of them deal with corneal involvement.

In the description of pterygium the author favors the theory that chronic inflammatory corneal ulceration is the precursor of pterygium formation with resulting conjunctival tendency to cover the defect of corneal substance. Dehiscences of Bowman's membrane and migration of keratoblasts are blamed for irreversible damage caused by edema of corneal epithelium and stroma of long standing. It is an important warning for the clinical ophthalmologist. Studies of conical corneas reveal histopathological lesions characteristic of this disease as follows: multiple dehiscences of Bowman's membrane overlying folds of the basal membrane in the ectatic area and invaginations of Descemet's membrane into the stroma.

According to sections from a case of marginal ketatectasia (maladie de Terrien) inflammatory process seems to present the underlying cause.

Epithelial proliferation originating from the edges of the corneal graft, especially

when the graft is placed in diseased corneal stroma, seems to be the cause of some failures in corneal transplants resulting in opacification of the graft.

Other articles deal with ocular tumors, retrolental fibroplasia, and pigmentary degeneration of the retina.

The book contains 60 plates with outstanding microphotographs. The author has also prepared an English translation of the complete book including a description of the microphotographs.—*George Z. Carter, M.D.*

Differential Diagnosis of Common Diseases of the Eyeground. PAUL TOWER. 242 pages. Grune & Stratton. $10.

This book is an outgrowth of the author's teaching experience of undergraduate students and as such is of greater interest to the beginner in ophthalmology than to the experienced ophthalmologist.

A chapter is devoted to each of these subjects—The Normal Fundus, Congenital Anomalies, Diseases of the Retina, Diseases of the Choroid, Diseases of the Macula, Glaucoma, Diseases of the Optic Nerve, and Myopia.

The text is, on the whole, well written and the captions of the illustrations complete and informative. A pleasing innovation is the insertion in pertinent locations of brief discussions of the literature on the subject at hand. An occasional statement such as "but it must always be remembered that distinction between beginning scotoma and refractive error is difficult and calls for the use of special equipment" may be open to discussion.

The author's decision to use no colored illustrations was an unfortunate one, for the black and white ones are in general poor. Those designed to demonstrate optic nerve changes are valueless and other conditions may be recognized with difficulty even by those who are familiar with them. The lack of good colored illustrations weighs heavily against the book's usefulness to students.

The book is recommended for the student in particular, though every practicing ophthalmologist will find much of value.—*Paul T. McAlpine, M.D.*

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1. Cass, L. J., and Frederik, W. S.: Ann. New York Acad. Sc. *58*:455 (July 15) 1954.

2. Shaftel, H. E.: J. Am. Geriatrics Soc. *1*:549 (Aug.) 1953.

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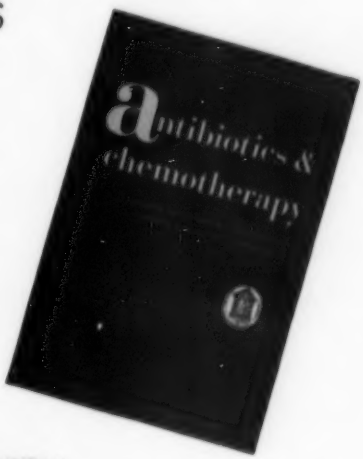

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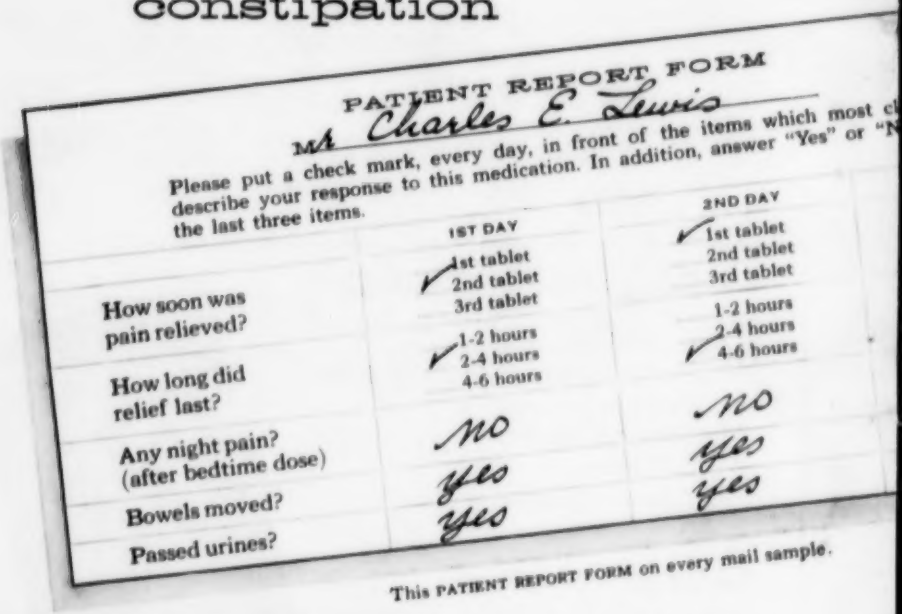

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how supplied Bottles of 100 scored tablets. There are 5 mg. of PIPTAL in each tablet. PIPTAL is the *only* brand of N-ethyl-3-piperidyl -benzilate methobromide.

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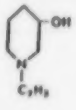

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